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PTO-1556
(5/87)

SOLID AND SOLUTION PHASE SYNTHESIS OF EPOTHILONES A AND B AND LIBRARIES OF EPOTHILONE ANALOGS

Specification

Technical Field of the Invention:

The present invention relates to epothilone A, epothilone B, epothilone analogs, libraries of epothilone analogs, and methods for producing such compounds using solid phase and solution phase chemistries.

Government Rights:

This invention was made with government support under Grants No. CA 6446 and CA 58336 awarded by the National Institutes of Health. The U.S. government has certain rights in the invention.

Background of the Invention:

Epothilone A (1, Figure 1) and epothilone B (2, Figure 1) are natural substances isolated from myxobacteria Sorangium cellulosum strain 90. These natural substances exhibit cytotoxicity against taxol-resistant tumor cells and may prove to have a clinical utility comparable or superior to Taxol. (For Taxol references see: Horwitz et al. Nature 277, 665-667 (1979); Nicolaou et al. Angew. Chem. Int. Ed. Engl. 33, 15-44 (1994).) Like taxol, the epothilones are thought to exert their cytotoxicity by induction of microtubule assembly and stabilization. (Bollag et al. Cancer Res. 55, 2325-2333 (1995); Kowalski et al. J. Biol. Chem. 272, 2534-2541 (1997).) Epothilones are reported to be about 2000-5000 times more potent

than Taxol with resp ct to the stabilization f microtubules. Despite the marked structural differences between the epothilones and Taxol™, the epothilones were found to bind to the same regi n on microtubules and to displace Taxol™ from its binding site. (Grever et al. Seminars in Oncology 1992, 19, 622-638; Bollag et al. Cancer Res. 1995, 55, 2325-2333; Kowalski et al. J. Biol. Chem. 1997, 272, 2534-2541; Horwitz et al. Nature 1979, 277, 665-667; Nicolaou et al. Angew. Chem. Int. Ed. Engl. 1994, 33, 15-44.) Epothilones A and B have generated intense interest amongst chemists, biologists and clinicians due to their novel molecular architecture, important biological action and intriguing mechanism of action. (Höfle et al. Angew. Chem. Int. Ed. Engl. 35, 1567-1569 (1996); Grever et al. Semin. Oncol. 19, 622-638 (1992); Bollag et al. Cancer Res. 55, 2325-2333, (1995); Kowalski et al. J. Biol. Chem. 272, 2534-2541 (1997); Nicolaou t al. Angew. Chem. Int. Ed. Engl. 35, 2399-2401 (1996); Meng et al. J. Org. Chem. 61, 7998-7999 (1996); Bertinato et al. J. Org. Chem. 61, 8000-8001 (1996); Schinzer et al. Chem. Eur. J. 2, 1477-1482 (1996); Mulzer et al. Tetrahedron Lett. 37, 9179-9182 (1996); Claus et al. Tetrahedron Lett. 38, 1359-1362 (1997); Gabriel et al. Tetrahedron Lett. 38, 1363-1366 (1997); Balog et al. Angew. Chem. Int. Ed. Engl. 35, 2801-2803 (1996); Yang et al. Angew. Chem. Int. Ed. Engl. 36, 166-168 (1997); Nicolaou et al. Angew. Chem. Int. Ed. Engl. 36, 525-527 (1997); Schinzer et al. Angew. Chem. Int. Ed. Engl. 36, 523-524 (1997); Meng et al. J. Am. Chem. Soc. 119, 2733-2734 (1997).)
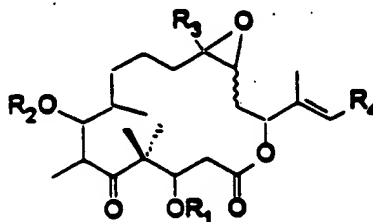
What is needed are analogs of epothilone A and B and libraries of analogs of epothilone A and B that exhibit superior pharmacological properties in the area of microtubule stabilizing

agents.

What is needed are methods for producing synthetic epothilone A, epothilone B, analogs of epothilone A and B, and libraries of epothilone analogs, including epothilone analogs possessing both optimum levels of microtubule stabilizing effects and cytotoxicity.

Brief Summary of the Invention:

A first mode of the invention is directed to a macrolactonization procedure for synthesizing epothilone and epothilone analogs represented by the following structure:
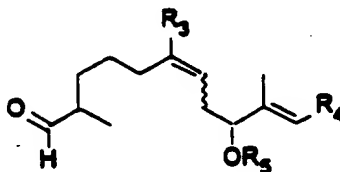

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:
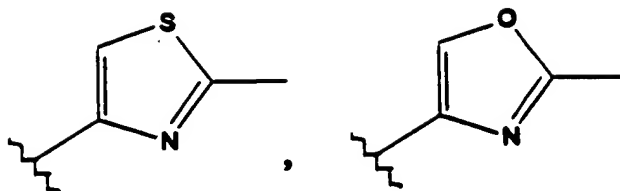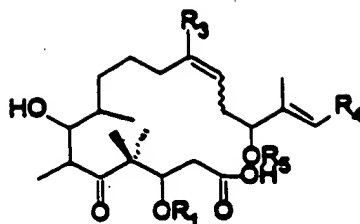
The synthesis may be initiated by condensing a keto acid represented by the following structure:
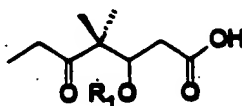
with an aldehyde represented by the following structure:

wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl, for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:

The synthesis is then continued by derivatizing the free hydroxyl moiety of the above carboxylic acid with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:
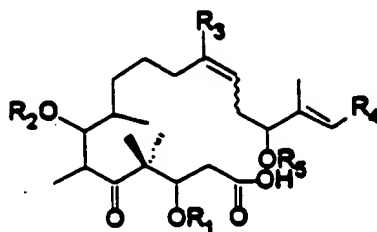
The R_5 protected hydroxyl moiety of the above derivatized carboxylic acid is then regioselectively deprotected for producing a hydroxy acid with the following structure:
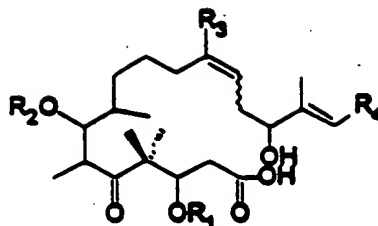
The above hydroxy acid is then macrolactonized for producing a macrolide with the following structure:
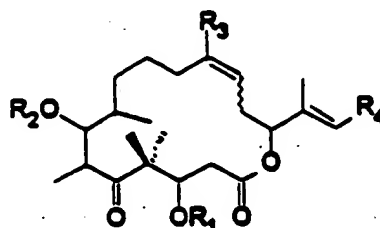
5

The synthesis is then completed by epoxidizing the above macrolide for producing the epothilone or epothilone analog.

Further aspects of the invention related to this first mode
10 are directed to each of the individual steps of the above synthetic macrolactionization procedure and to each of the chemical intermediates employed therein.

A second mode of the invention is directed to a metathesis
15 approach to synthesizing epothilone and epothilone analogs represented by the following structure:

- 6 -

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:
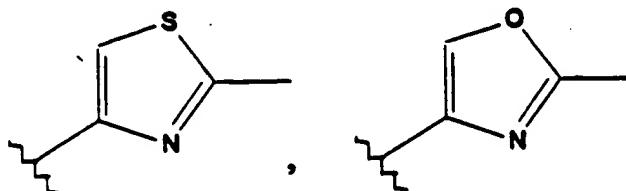
The synthetic protocol is initiated by condensing a keto acid represented by the following structure:
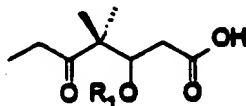
with an aldehyde represented by the following structure:

- 7 -

$$R_3 \diagup\!\!\!\diagdown\!\!\!\diagup\!\!\!\diagdown\!\!\!\diagup^{O}$$

wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$-(solid phase support), for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:
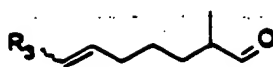
$$\text{HO} \cdots \diagup\!\!\!\diagdown R_3 \text{ COOH, OR}_1, O$$
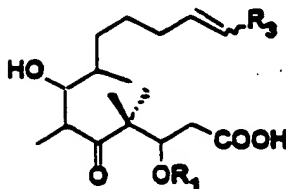
Alternative preferred solid supports include Merrifield resin, PEG-polystyrene, hydroxymethyl polystyrene, formyl polystyrene, aminomethyl polystyrene, and phenolic polystyrene.

The above carboxylic acid is then esterified with a secondary alcohol represented by the following structure:
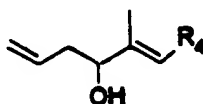
$$\diagup\!\!\!\diagdown\!\!\!\diagup\!\!\!\diagdown^{R_4}_{OH}$$

for producing an ester with a free hydroxyl moiety represented by the following structure:
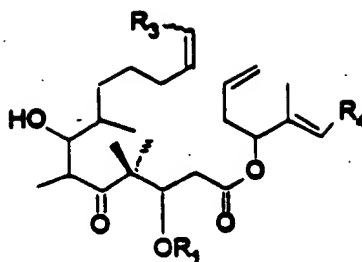
The synthesis is then continued by derivatizing the free hydroxyl moiety of the above ester with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized ester represented by the following structure:
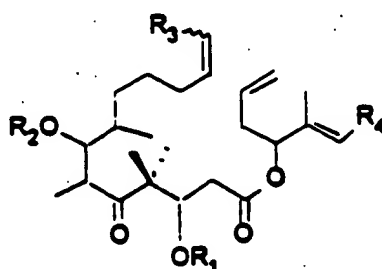
The above derivatized ester is then metathesized with an

organo-m tallic catalyst f r pr ducing a macr lide with the following structure:
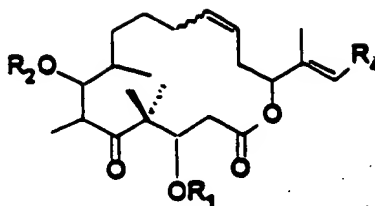
Preferred organo-metallic catalyst include bis(tricyclohexylphosphine)benzylidine ruthenium dichloride and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

The above macrolide is then epoxidized for producing the epothilone analog.

Further aspects of the invention related to this second mode are directed to each of the individual steps of the above synthetic metathesis procedure and to each of the chemical intermediates employed therein.

A third mode of the invention is directed to a metathesis approach to synthesizing an epothilone analog represented by the following structure:
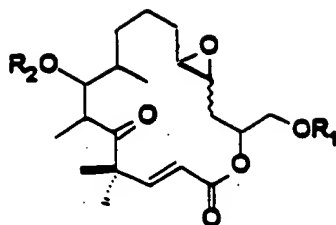
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:
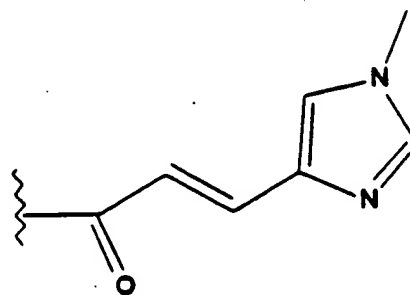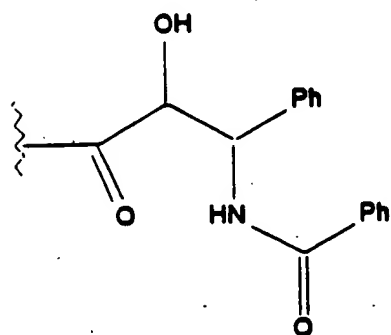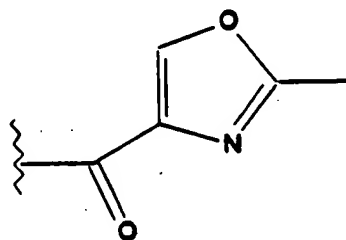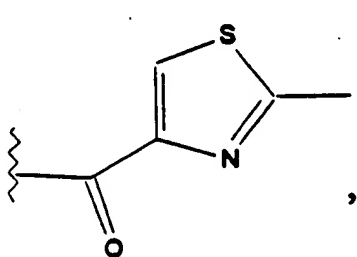
and wherein R₂ is selected from the group c nsisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl.

The synthesis is initiated by esterifying a keto acid represented by the following structure:
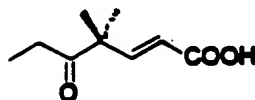
with an alcohol represented by the following structure:
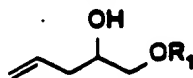
for producing an ester represented by the following structure:

5   Then, the above ester is condensed with an aldehyde represented by the following structure:
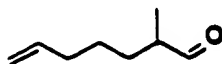
- 12 -

for producing a bis-terminal olefin with the following structure:

The synthesis is then continued by metathesizing the above bis-terminal olefin with an organo-metallic catalyst for producing a macrocyclic lactone with a free hydroxyl moiety represented by the following structure:
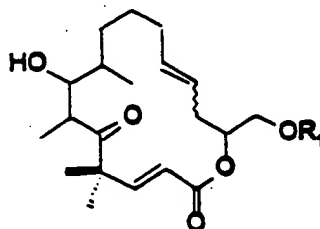

Preferred organo-metallic catalysts include bis(tricyclohexylphosphine)benzylidine ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

The free hydroxyl of the above macrocyclic lactone is then derivatized with a derivatizing age... . epresented by the formula

R$_2$-X wh r in R$_2$-X is selected from th gr up consisting f hydrogen, *tert*-butyldimethylsilyl chloride, *tert*-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(*tert*-butoxycarbonyloxyimíno)-2-phenylacetonitrile for producing a derivatized macrolide with the following structure:
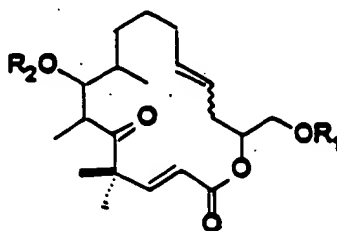
The synthesis is then completed by epoxidizing the above derivatized macrolide for producing the epothilone analog.

Further aspects of the invention related to this third mode are directed to each of the individual steps of the above synthetic metathesis procedure and to each of the chemical intermediates employed therein.

A fourth mode of the invention is directed to a method employing a metathesis approach for synthesizing an epothilone analog represented by the following structure:
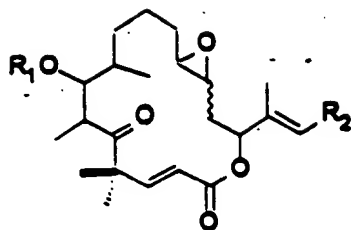
- 14 -

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following structures:
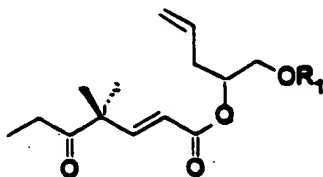

The synthesis is initiated by condensing a keto acid represented by the following structure:

with an aldehyde represented by the following structure:

- 15 -
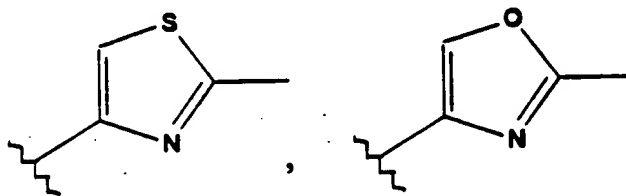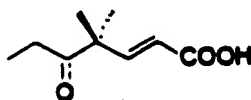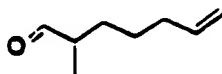
for producing a carboxylic acid with a free hydr xyl moiety represented by the following structure:
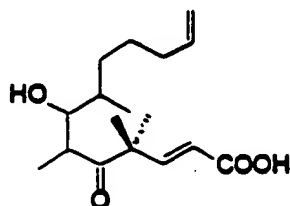
The free hydroxyl moiety of the above carboxylic acid is then derivatized with a derivatizing agent represented by the formula R_1-X wherein R_1-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:
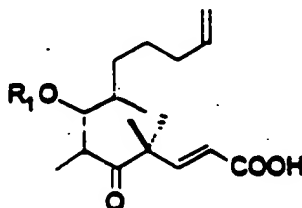
The synthesis is then continued by esterifying the
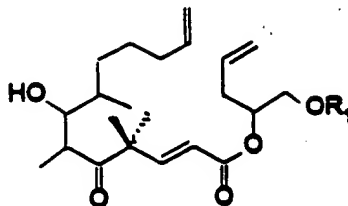
derivatized carboxylic acid of said Step B with an alcohol
represented by the following structure:
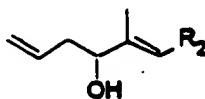
for producing a bis-terminal olefin with the following structure:
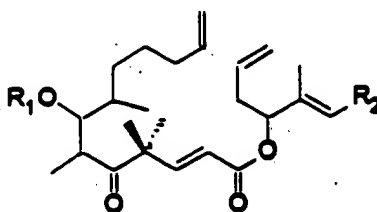
The above bis-terminal olefin is then metathesized with an
organo-metallic catalyst for producing a macrocyclic lactone with
the following structure: .
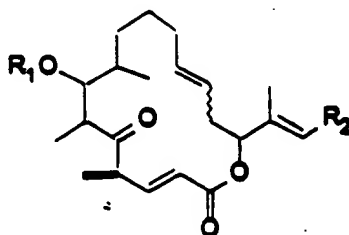
Preferred organo-metallic catalysts include

bis(tricycl hexylphosphine)benzylidine ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

The synthesis is then completed by epoxidizing the above macrocyclic lactone for producing the epothilone analog.

Further aspects of the invention related to this fourth mode are directed to each of the individual steps of the above synthetic metathesis procedure and to each of the chemical intermediates employed therein.

A fifth mode of the invention is directed to a method employing a macrolatonization approach for synthesizing an epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$,

-CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R$_4$ is selected from the group represented by the formulas:

,

The synthesis is initiated by condensing a keto acid represented by the following structure:

wherein R$_6$ is selected from the group consisting of *tert-butyldimethylsilyl*, *trimethylsilyl*, *tert-butyldiphenylsilyl*, methyl, hydrogen, *triethylsilyl*, and benzyl; with an aldehyde represented by the following structure:

wherein R$_5$ is selected from the group consisting of *tert-*

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butyldimethylsilyl and trimethylsilyl, for producing a β-hydroxy ketone with a free hydroxyl moiety and a R_4 protected hydroxyl moiety represented by the following structure:
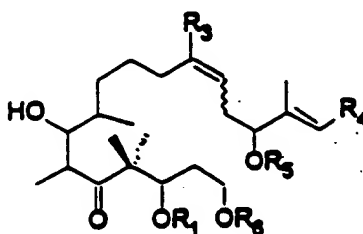
The free hydroxyl moiety of the above β-hydroxy ketone is then derivatized with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized β-hydroxy ketone represented by the following structure:
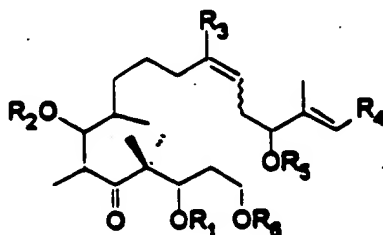
The R_4 protected hydroxyl moiety of the above derivatized β-

hydr xy ket n   is then regioselectively deprotected f r producing
a terminal alcohol with the following structure:

R_2O ... R_3 ... R_4 ... OR_5 ... OR_1 OH ... O
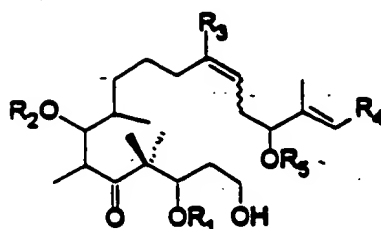
5   The above terminal alcohol is then oxidized for producing a
derivatized carboxylic acid with a R_5 protected hydroxyl moiety
with the following structure:

R_2O ... R_3 ... R_4 ... OR_5 OH ... OR_1 O ... O
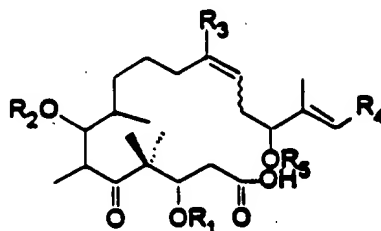
10   The synthesis is then continued by regioselectively
deprotecting the R_5 protected hydroxyl moiety of the derivatized
carboxylic acid of said step D for producing a hydroxy acid with
the following structure:
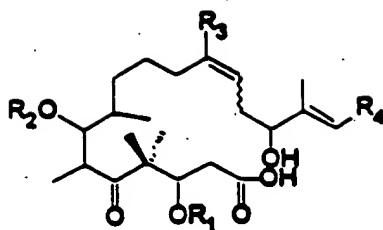
The above hydroxy acid is then macrolactonized for producing a macrolide with the following structure:
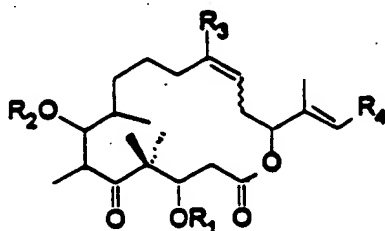
The synthesis is then completed by epoxidizing the above macrolide for producing the epothilone analog.

Further aspects of the invention related to this fifth mode are directed to each of the individual steps of the above synthetic macrolactonization procedure and to each of the chemical intermediates employed therein.

A sixth mode of the invention is directed to the use of each of the above metathesis approaches for synthesizing libraries of epothilone analogs. In this mode, a combinatorial approach is employed for synthesizing libraries of epothilone analogs having

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various combinations of the preferred R groups.

various c mbinati ns of the preferred R groups.

Description of Figures:

Figure 1 illustrates the structure and numbering of epothilone A (1) and B (2).

Figure 2 illustrates the retrosynthetic analysis of the natural product compound epothilone A (1).

Figure 3 illustrates the synthesis of 3 building block substrates wherein A) represents the synthesis of aldehyde 7 with reagents and conditions as follows: (a) 1.05 equivalents of NaHMDS, 2.0 equivalents of n-C5H9I, 3.0 equivalents HMPA, -78 to 25°C , 5 hours; (b) 1.1 equivalents of LiAlH$_4$, THF, -78°C, 15 minutes, 60% (2 steps); (c) 1.5 equivalents of NMO, 5 mol % of TPAP, Methylene chloride, 4 Å MS, 25°C, 0.5 hour, 95%. NaHMDS = sodium bis(trimethylsilyl)amide; HMPA = hexamethylphosphoramide, NMO = 4-methylmorpholine-N-oxide; TPAP = tetrapropyl ammonium perruthenate; B) represents the synthesis of alcohols 18a and 18b. Reagents and conditions: (a) 1.3 equivalents of TPSCl, 2.0 equivalents of imidazole, DMF, 0 to 25°C, 1.5 hours (90% of 17a, 94% of 17b); (b) 1.25 equivalents of tetravinyltin, 5.0 equivalents of n-BuLi, THF, -78°C, 45 minutes, then 2.5 equivalents of CuCN in THF, -78 to -30°C; then 17a or 17b in THF, -30°C, 1 hour, 18a (86%), 18b (83%) (TPS - ...h$_2$tBu); C) represents the synthesis of ketoacid 2). Reagents and conditions: (a) 1.2 equivalents o. ...va. ..6 equivalents of NaH,

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THF, 0 - 25°C, 1 hour, 99%; (b) CF₃COOH:Methylene chloride (1:1), 25°C, 0.5 hour, 99%.

Figure 4 illustrates the synthesis of the epothilone cyclic framework via olefin metathesis: the 15*S* series. Reagents and conditions: (a) 1.2 equivalents of EDC, 0.1 equivalent of 4-DMAP, Methylene chloride, 0 - 25°C, 12 hours, 86%; (b) **21**, 1.2 equivalents of LDA, -78°C - -40°C, THF, 45 minutes; then 1.6 equivalents of **7** in THF, -78 - -40°C, 0.5 hour, **23** (42%), **24** (33%); (c) 0.1 equivalent of RuCl₂(=CHPh)(PCy₃)₂, Methylene chloride, 25°C, 12 hours, **25** (85%), **26** (79%); (d) 2.0 equivalents of TBAF, 5.0 equivalents of AcOH, 25°C, 36 hours, **27** (92%), **28** (95%). DCC = dicyclohexylcarbodiimide, 4-DMAP = 4-dimethylaminopyridine, LDA = lithium diisopropylamide.

Figure 5 illustrates the synthesis of the epothilone cyclic framework via olefin metathesis: the 15*R* series. Reagents and conditions: (a) 1.4 equivalents of DCC, 1.4 equivalents of 4-DMAP, toluene, 25°C, 12 hours, 95%; (b) **21**, 1.2 equivalents of LDA, -78°C - -40°C, THF, 45 minutes; then 1.6 equivalents of **7** in THF, -78 - -40°C, 0.5 hour, **29** (54%), **30** (24%); (c) 0.1 equivalent of RuCl₂(=CHPh)(PCy₃)₂, Methylene chloride, 25°C, 12 hours, **31** (80%), **32** (81%).

Figure 6 illustrates the metathesis approach and epoxidation in the presence of thiazole: synthesis of epothilone analogs 39-44. Metathesis and epoxidation in the presence of thiazole: synthesis of epothilo... gs 39-44. Reagents and conditions:

(a) 21, 2.3 equivalents of LDA, -78 - -30°C, THF, 1.5 hours; then 1.6 equivalents of 7 in THF, -78 - -40°C, 1 hour (33:34, 2:3); (b) ca 2.0 equivalents of 6, ca 1.2 equivalents of EDC, ca 0.1 equivalent of 4-DMAP, Methylene chloride, 0 - 25°C, 12 hours, 35 (29%), 6 (44%) (2 steps); (c) 0.1 equivalent of $RuCl_2(=CHPh)(PCy_3)_2$, Methylene chloride, 25°C, 12 hours, 7 (86%), 38 (66%); (d) 0.9-1.2 equivalents of mCPBA, $CHCl_3$, -20 - 0°C, 12 hours, 37 - 39 (or 40) (40%), 40 (or 39) (25%), 41 (18%); 38 - 42 (or 43) (22%), 43 (or 42) (11%), 44 (7%); (e) excess of CF_3COCH_3, 8.0 equivalents of $NaHCO_3$, 5.0 equivalents of Oxone®, CH_3CN/Na_2EDTA (2:1), 0°C, 37 - 39 (or 40) (45%), 40 (or 39) (28%); 38 - 42 (or 43) (60%), 43 (or 42) (15%). mCPBA = meta-Chloroperbenzoic acid.

Figure 7 illustrates the coupling of building blocks 6-8. Reagents and conditions: (a) 8, 2.3 equivalents of LDA, -78 - -30°C, THF, 1.5 hours; then 1.6 equivalents of 7 in THF, -78 - -40°C, 1 hour (45:46, 3:2); (b) ca 2.0 equivalents of 6, ca 1.2 equivalents of EDC, ca 0.1 equivalent of 4-DMAP, Methylene chloride, 0 - 25°C, 12 hours, 4 (52%), 47 (31%) (2 steps).

Figure 8 illustrates the epoxidation of epothilone framework: total synthesis of epothilone A (1) and analogs 51-57. Epoxidation of epothilone framework: total synthesis of epothilone A (1) and analogs 51-57. (a) 0.1 equivalent of $RuCl_2(=CHPh)(PCy_3)_2$, Methylene chloride, 25°C, 20 hours, 3 (46%), 48 (39%); (b) 20% CF_3COOH in Methylene chloride, 0°C, 3 hours, 3 - 49 (90%); 48 - 50 (92%); (c) 0.8-1.2 equivalents of mCPBA,

CHCl$_3$, -20 - 0°C, 12 hours, 49 - 1 (35%), 51 (13%), 52 (or 53) (9%), 53 (or 52) (7%), 54 (or 55) (5%), 55 (or 54) (5%); 1 - 54 (or 55) (35%%), 55 (or 54) (33%), 57 (6%); (d) 1.3-2.0 equivalents of mCPBA, CHCl$_3$, -20 - 0°C, 12 hours, 1 (15%), 51 (10%), 52 (or 53) (10%), 53 (or 52) (8%), 54 (or 55) (8%), 55 (or 54) (7%), 56 (5%), 57 (5%); (e) 1.0 equivalent of dimethyldioxirane, CH$_2$Cl$_2$/acetone, 0°C, 1 (50%), 51 (15%), 52 (or 53) (5%), 53 (or 52) (5%); (f) excess of CF$_3$COCH$_3$, 8.0 equivalents of NaHCO$_3$, 5.0 equivalents of Oxone®, CH$_3$CN/Na$_2$EDTA (2:1), 0°C, 1 (62%), 51 (13%).

Figure 9 illustrates the synthesis of epothilones 58-60. Reagents and conditions: (a) 0.9-1.3 equivalents of mCPBA, CHCl$_3$, -20 - 0°C, 12 hours, 58 (or 59) (5%), 59 (or 58) (5%), 60 (60%); (b) 1.0 equivalent of dimethyldioxirane, Methylene chloride/acetone, 0°C, 58 (or 59) (10%), 59 (or 58) (10%), 60 (40%); (c) excess of CF$_3$COCH$_3$, 8.0 equivalents of NaHCO$_3$, 5.0 equivalents of Oxone®, MeCN/Na$_2$EDTA (2:1), 0°C, 58 (or 59) (45%), 59 (or 58) (35%).

Figure 10 illustrates the synthesis of epothilones 64-69. (a) 20% CF$_3$COOH in Methylene chloride, 0°C, 3 hours, 90%; (b) 0.1 equivalent of RuCl$_2$(=CHPh)(PCy$_3$)$_2$, Methylene chloride, 25°C, 20 hours, 62 (20%), 63 (69%); (c) 0.8-1.2 equivalents of mCPBA, CHCl$_3$, -20 - 0°C, 12 hours, 62 - 64 (or 65) (25%), 65 (or 64) (23%); 63 - 67 (or 68) (24%), 68 (or 67) (19%), 69 (31%); (d) excess of CF$_3$COCH$_3$, 8.0 equivalents of NaHCO$_3$, 5.0 equivalents of Oxone®, CH$_3$CN/Na$_2$EDTA (2:1), 0°C, 62 - 64 (or 65) (58%), 65 (or 64) (29%); 63 - 67 (or 68) (44%), 68 (or 67) (21%).

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Figure 11 illustrates th molecular structures and retrosynthetic analysis of epothilones A (1) and B (2) using the macrolactonization approach.

Figure 12 illustrates the synthesis of 2 building block substrates wherein A) represents the synthesis of keto acid 76. Reagents and conditions: (a) 1.2 equivalents of (+)-Ipc₂B(allyl), Et₂O, -100°C, 0.5 hour, 74% (ee >98% by Mosher ester analysis); (b) 1.1 equivalents TBSOTf, 1.2 equivalents of 2,6-lutidine, Methylene chloride, 25°C, 98% ; (c) O₃, Methylene chloride, -78°C, 0.5 hour; then 1.2 equivalents Ph₃P, -78 - 25°C, 1 hour, 90%; (d) 3.0 equivalents of NaClO₂, 4.0 equivalents of 2-methyl-2-butene, 1.5 equivalents of NaH₂PO₄, tBuOH:H₂O (5:1), 25°C, 2 hours, 93%; B) represents the synthesis of phosphonium salt 79 and aldehyde 82. Reagents and conditions: (a) 1.6 equivalents of DIBAL, Methylene chloride, -78°C, 2 hours, 90%; (b) Ph₃P=C(CH₃)CHO, benzene, reflux, 98%; (c) 1.5 equivalents of (+)-Ipc₂B(allyl), Et₂O, -100°C, 0.5 hour, 96% (ee >97% by Mosher ester analysis); (d) 1.2 equivalents TBSCl, 1.5 equivalents of imidazole, DMF, 0 - 25°C, 2 hours, 99%; (e) i. 1.0 mol % OsO₄, 1.1 equivalents of 4-methylmorpholine N-oxide (NMO), THF:tBuOH:H₂O (1 : 1 : 0.1), 0 - 25°C, 12 hours, 95%; ii. 1.3 equivalents of Pb(OAc)₄, EtOAc, 0°C, 0.5 hour, 98%; (f) 2.5 equivalents of NaBH₄, MeOH, 0°C, 15 minutes, 96%; (g) 1.5 equivalents of I₂, 3.0 equivalents of imidazole, 1.5 equivalents of Ph₃P, Et₂O:MeCN (3 : 1), 0°C, 0.5 hour, 89%; g. 1.1 equivalents Ph₃P, neat, 100°C, 2 hours, 98%.

Figure 1 illustrates the synthesis of aldehyde and

ketone 78. Reagents and conditions: (a) 1.1 equivalents of LDA, THF, 0°C, 8 hours; then 1.5 equivalents of 4-iodo-1-benzyloxybutane in THF, at -100 - 0°C, 6 hours, 92% (de >98% by ^{1}H NMR); (b) O_3, Methylene chloride, -78°C, 77% or MeI, 60°C, 5 hours; then 3 N aq HCl, n-pentane, 25°C, 1 hour, 86%; (c) 3.0 equivalents of NaBH$_4$, MeOH, 0°C, 15 minutes, 98%; (d) 1.5 equivalents of TBSCl, 2.0 equivalents of Et$_3$N, Methylene chloride, 0 - 25°C, 12 hours, 95%; (e) H$_2$, Pd(OH)$_2$ cat., THF, 50 psi, 25°C, 15 minutes, 95%; (f) 2.0 equivalents of (COCl)$_2$, 4.0 equivalents of DMSO, 6.0 equivalents of Et$_3$N, Methylene chloride, -78 - 0°C, 1.5 hours, 98%; (g) 1.5 equivalents of MeMgBr, THF, 0°C, 15 minutes, 84%; (h) 1.5 equivalents of NMO, 0.05 equivalent of tetra-i-propylammonium perruthenate (TPAP), 4Å MS, Methylene chloride, 25°C, 45 minutes, 96%.

Figure 14 illustrates the total synthesis of epothilone A (1) and its 6S,7R-diastereoisomers (111 and 112). Reagents and conditions: (a) 1.2 equivalents of 79, 1.2 equivalents of NaHMDS, THF, 0°C, 15 minutes, then add 1.0 equivalent of aldehyde 77, 0°C, 15 minutes, 77% (Z : E ca. 9 : 1); (b) 1.0 equivalent of CSA portionwise over 1 hour, Methylene chloride:MeOH (1 : 1), 0 - 25°C, 0.5 hour, 86%; (c) 2.0 equivalents of SO$_3$.pyr., 10.0 equivalents of DMSO, 5.0 equivalents of Et$_3$N, Methylene chloride, 25°C, 0.5 hour, 94%; (d) 3.0 equivalents of LDA, THF, 0°C, 15 minutes; then 1.2 equivalents of 76 in THF, -78 - -40°C, 0.5 hour; then 1.0 equivalent of 74 in THF at -78°C, high yield of 103a and its 6S,7R-diastereoisomer 103b (ca. 1 : 1 ratio); (e) 3.0 equivalents of TBSOTf, 5.0 equivalents of 2,6-lutidine, Methyl e chloride, 0°C, 2 hours; (f) 2.0 e. valents of K$_2$CO$_3$,

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MeOH; 25°C, 15 minutes, 31% _f 105 and 30%¯of 6S,7R-
diastereoisomer 106 from 74; (g) 6.0 equivalents of TBAF, THF,
25°C, 8 hours, 78%; (h) same as g, 82%; (i) 5.0 equivalents of
2,4,6-trichlorobenzoylchloride, 6.0 equivalents of Et₃N, THF,
25°C, 15 minutes; then add to a solution of 10.0 equivalents of
4-DMAP in toluene (0.002 M based on 72), 25°C, 0.5 hour, 90%; (j)
same as i, 85%; (k) 20% CF₃COOH (by volume) in Methylene
chloride, 0°C, 1 hour, 92%; (l) same as k, 95%; (m)
methyl(trifluoromethyl)dioxirane, MeCN, 0°C, 75% (ca 5:1 ratio
of diastereoisomers); (n) same as m, 87% (111 : 112 ca 2 : 1
ratio of diastereoisomers, tentative stereochemistry).

Figure 15 illustrates the synthesis of compound 101.
Reagents and conditions: (a) 1.5 equivalents of I₂, 3.0
equivalents of imidazole, 1.5 equivalents of Ph₃P, Et₂O:MeCN (3 :
1), 0°C, 0.5 hour, 91%; (b) 1.1 equivalents Ph₃P, neat, 100°C, 2
hours, 91%; (c) 1.2 equivalents of 114, 1.2 equivalents of
NaHMDS, THF, 0°C, 15 minutes; then add 1.0 equivalent of aldehyde
82, 0°C, 15 minutes, 69% (Z : E ca 9 : 1).

Figure 16 illustrates the total synthesis of epothilone B
(2) and analogs. Reagents and conditions: (a) 1.5 equivalents of
79, 1.5 equivalents of NaHMDS, THF, 0°C, 15 minutes, then add 1.0
equivalent of ketone 78, -20°C, 12 hours, 73% (Z : E ca 1 : 1);
(b) 1.0 equivalent of CSA portionwise over 1 hour, Methylene
chloride:MeOH (1 : 1), 0°C; then 25°C, 0.5 hour, 97%; (c) 2.0
equivalents of SO₃.pyr., 10.0 equivalents of DMSO, 5.0
equivalents of Et₃N, Methylene chloride, 25°C, 0.5 hour, 95%;
3.0 equivalents of LDA, THF, 0°C, 15 minutes; then 1.2

equivalents *f* 76 in THF, -78 - -40°C, 0.5 hour; then 1.0 equivalent of 75' in THF at -78°C, high yield of 117a' and its 6S,7R-diastereoisomer 117b' (*ca* 1 : 1 ratio); (e) 3.0 equivalents of TBSOTf, 5.0 equivalents of 2,6-lutidine, Methylene chloride, 0°C, 2 hours; (f) 2.0 equivalents of K_2CO_3, MeOH, 25°C, 15 minutes, 31% of 119' and 30% of 6S,7R-diastereoisomer 120' from 75'; (g) 6.0 equivalents of TBAF, THF, 25°C, 8 hours, 75%; (h) 1.3 equivalents of 2,4,6-trichlorobenzoylchloride, 2.2 equivalents of Et_3N, THF, 0°C, 1 hour; then add to a solution of 10.0 equivalents of 4-DMAP in toluene (0.002 M based on 73'), 25°C, 12 hours, 37% of 121; and 40% of 122; (i) 20% CF_3COOH (by volume) in Methylene chloride, -10 - 0°C, 1 hour, 91%; (j) same as *i*, 89%; (k) dimethyldioxirane, Methylene chloride, -50°C, 75% (2 : 124 *ca* 5 : 1 ratio of diastereoisomers) or 1.5 equivalents of *m*CPBA, benzene, 3°C, 2 hours, 66% (2 : 124 *ca* 5 : 1 ratio of diastereoisomers) or methyl(trifluoromethyl)dioxirane, MeCN, 0°C, 85% (2 : 124 *ca* 5 : 1 ratio of diastereoisomers); (l) 1.5 equivalents *m*CPBA, benzene. 3°C, 2 hours, 73% (125 : 126 *ca* 4 : 1 ratio of stereoisomers) or methyl(trifluoromethyl)dioxirane, MeCN, 0°C, 86% (125 : 126 *ca* 1 : 1 ratio of diastereoisomers).

Figure 17 illustrates the stereoselective synthesis of aldehyde 75 for epothilone B (2). Reagents and conditions: (a) 1.5 equivalents of 83, benzene, reflux, 5 hours, 95%; (b) 3.0 equivalents of DIBAL, Methylene chloride, -78°C, 2 hours, 98%; (c) 2.0 equivalents of Ph_3P, CCl_4, reflux, 24 hours, 83%; (d) 2.0 equivalents of $LiEt_3BH$, THF, 0°C, 1 hour, 99%; (e) 1.2 equivalents of 9-BBN, THF, 0°C, 2 hours, 91%; (f) equivalents of I_2, 3.0 equivalents of imidazole, 1.5 equivalents

of Ph₃P, Et₂O:MeCN (3 : 1), 0°C, 0.5 hour, 92%; (g) 1.5
equivalents of 80, 1.5 equivalents of LDA, THF, 0°C, 8 hours;
then 1.0 equivalent of 81 in THF, -100 - -20°C, 10 hours, 70%;
(h) 2.5 equivalents of monoperoxyphthalic acid, magnesium salt
(MMPP), MeOH:phosphate buffer pH7 (1:1), 0°C, 1 hour , 80%; (i)
2.0 equivalents DIBAL, toluene, -78°C, 1 hour, 82%.

Figure 18 illustrates the first stereoselective total
synthesis of epothilone B (2). Reagents and conditions: (a) 3.0
equivalents of LDA, THF, 0°C, 15 minutes; then 1.2 equivalents of
76 in THF, -78 - -40°C, 0.5 hour, then 1.0 equivalent of 75 in
THF at -78°C, high yield of 117a and 6S,7R-diastereoisomer 117b
(ca 1.3 : 1.0 ratio of diastereoisomers); (b) 3.0 equivalents of
TBSOTf, 5.0 equivalents of 2,6-lutidine, Methylene chloride, 0°C,
2 hours; (c) 2.0 equivalents of K₂CO₃, MeOH, 25°C, 15 minutes,
32% of 119 and 28% of 6S,7R-diastereoisomer 119 from 75; (d) 6.0
equivalents of TBAF, THF, 25°C, 8 hours, 73%; (e) same as d, 71%;
(f) 5.0 equivalents of 2,4,6-trichlorobenzoylchloride, 6.0
equivalents of Et₃N, THF, 25°C, 15 minutes, then add to a
solution of 10.0 equivalents of of 4-DMAP in toluene (0.002 M
based on 73), 25°C, 12 hours, 77%; (g) same as f, 76%; (h) 20%
CF₃COOH (by volume) in Methylene chloride, 0°C, 1 hour, 91%; (i)
see Figure 16.

Figure 19 illustrates the second stereoselective synthesis
of epothilone B (2). Reagents and conditions: (a) 1.2
equivalents of LDA, THF, 0°C, 15 minutes; then 1.2 equivalents of
136 in THF, -78 - -40°C, 1 hour; then 1.0 equivalent of 75 in THF
at -78°C, 85% of 137 and 6S,7R-diastereoisomer 138 (ca 3 : 1

ratio); (b) 1.2 equivalents of TBSOTf, 2.0 equivalents of 2,6-lutidine, Methylene chloride, 0°C, 2 hours, 96%; (c) 1.0 equivalent of CSA portionwise over 1 hour, Methylene chloride:MeOH (1 : 1), 0 - 25°C, 0.5 hour, 85%; (c) 2.0 equivalents of $(COCl)_2$, 4.0 equivalents of DMSO, 6.0 equivalents of Et_3N, Methylene chloride, -78 - 0°C, 1.5 hours, 95%; (d) 3.0 equivalents of $NaClO_2$, 4.0 equivalents of 2-methyl-2-butene, 1.5 equivalents of NaH_2PO_4, tBuOH:H_2O (5:1), 25 °C, 2 hours, 90%.

Figure 20 illustrates the retrosynthetic analysis of epothilone A (1) by a solid phase olefin metathesis strategy wherein TBS = t-BuMe$_2$Si; filled circle = polystyrene.

Figure 21 illustrates the solid phase synthesis of epothilone a wherein: (a) 1,4-butanediol (5.0 eq.), NaH (5.0 eq.), n-Bu$_4$NI (0.1 eq.), DMF, 25°C, 12 hours; (b) Ph$_3$P (4.0 eq.), I$_2$ (4.0 eq.), imidazole (4.0 eq.), Methylene chloride, 25°C, 3 hours; (c) Ph$_3$P (10 eq.), 90°C, 12 hours (>90 % for 3 steps based on mass gain of polymer); (d) NaHMDS (3.0 eq.), THF:DMSO (1:1), 25°C, 12 hours; (e) 149 (2.0 eq.), THF, 0°C, 3 hours (>70% based on aldehyde recovered from ozonolysis); (f) 10% HF·pyridine in THF, 25°C, 12 hours; (g) (COCl)$_2$ (4.0 eq.), DMSO (8.0 eq.), Et$_3$N (12.5 eq.), -78 - 25°C (ca. 95% for 2 steps)*; (h) 144 (2.0 eq.), LDA (2.2 eq), THF, -78 - -40°C, 1 hour; then add resulting enolate to the resin suspended in a ZnCl$_2$ (2.0 eq.) solution in THF, -78 --40 oC, 2.0 hours (ca. 90%)*; (i) 143 (5.0 eq.), DCC (5.0 eq), 4-DMAP (5.0 eq.), 25°C, 15h (80% yield as determined by recovered heterocycle fragments obtained by treatment with NaOMe); (j) 153 (0.75 eq.), Me   e

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chloride, 25°C, 48 hours (52%; 154:155:156:141 = ca. 3:3:1:3);
(k) 20% TFA in Methylene chloride (v/v), 92% for 157 and 90% for
158; (l) 160 [methyl(trifluoromethyl)dioxirane], MeCN, 0°C, 2
hours (70 % for 1, 45 % for 159; in addition to these products,
the corresponding α-epoxides were also obtained). NaHMDS =
sodium bis(trimethylsilyl)amide; DMSO = dimethyl sulfoxide; LDA =
lithium diisopropylamide; TBS = t-BuMe$_2$Si; 4-DMAP = 4-
dimethylaminopyridine. * Estimated yield. The reaction was
monitored by infrared (IR) analysis of polymer-bound material and
by TLC analysis of the products obtained by ozonolysis.

Figure 22 illustrates activity of epothilones on tubulin
assembly. Reaction mixtures contained purified tubulin at 1.0
mg/ml, 0.4 M monosodium glutamate, 5% dimethyl sulfoxide, and
varying drug concentrations. Each compound was evaluated in
three diffrerent experiments and average values are shown.
Samples were incubated, centrifuged, and processed at room
temperature (dark circle = 71, EC$_{50}$ = 3.3 ± 0.2 µM; dark triangle
= 2, EC$_{50}$ = 4.0 ± 0.1 µM; open circle = 1, EC$_{50}$ = 14 ± 0.4 µM;
open square = taxol, EC$_{50}$ = 15. ± 2 µM; open triangle = 125, EC$_{50}$
= 22 ± 0.9 µM; dark square = 158, EC$_{50}$ = 25 ± 1 µM; open upside
down triangle = 123, EC$_{50}$ = 39 ± 2 µM. The EC$_{50}$ is defined as the
drug concentration that causes 50% of the tubulin to assemble
into polymer. In the absence of drug, less than 5% of the
tubulin was removed by centrifugation, while with high
concentrations of the most active drugs, over 95% of the protein
formed polymer. This suggests that at least 90% of the tubulin
had the potential to interact with epothilone and taxoids.
Although the EC$_{50}$ value obtained for Taxol was higher than that

obtained in an alternate assay as described in Hofle et al. *Angew. Chem. Int. Ed. Engl* 35, 1567-1569 (1996), the agent's role in these experiments was only as a control.

Figure 23 provides a table of results from cytotoxicity experiments with 1A9, 1A9PTX10 (β-tubulin mutant), 1A9PTX22 (β-tubulin mutant) and A2780AD cell lines showing relative activities of epothilones A (1) and B (2) as compared with synthetic analogues 71, 158, 123 and 125 as inducers of tubulin assembly and inhibitors of human ovarian carcinoma cell growth. (a) See Figure 22; (b) The growth of all cells lines was evaluated by quantitation of the protein in microtiter plates. The parental cell line 1A9, a clone of the A2780 cell line, was used to select two Taxo'-resistant sublines (1A9PTX10 and 1A9PTX22). These sublines were selected by growth in the presence of Taxol and verapamil, a P-glycoprotein modulator. Two distinct point mutations in the β-tubulin isotype M40 gene were identified. In 1A9PTX10 amino acid residue 270 was changed from Phe (TTT) to Val (GTT), and in 1A9PTX22 residue 364 was changed from Ala (GCA) to Thr (ACA). The A2780AD line is a multidrug resistant (MDR) line expressing high levels of P-glycoprotein. Relative resistance refers to the ratio of the IC_{50} value obtained with a resistant cell line to that obtained with the parental cell line.

Figure 24 illustrates the structure and numbering of epothilone A (1) and epoxalone A (2).

Figure 25 illustrates the coupling of building blocks and

construction of precursors 164 and 165. Reagents and conditions: (a) 2.4 equivalents of LDA, -40°C, THF, 1.5 hours, then 7 in THF, -40°C, 0.5 hour; 94% (45:46 *ca* 5:3); (b) 1.2 equivalents of (+)-Ipc$_2$B(allyl), Et$_2$O, -100 °C, 0.5 hour, 91%; (c) 2.0 equivalents of 163, 1.5 equivalents of DCC, 1.5 equivalents of 4-DMAP, toluene, 25°C, 12 hours, 49%(164) plus 33%(165) for two steps. TBS = *tert*-butyldimethylsilyl; Ipc$_2$B(allyl) = diisopinocampheylallyl borane; LDA = lithium diisopropylamide; DCC = dicyclohexylcarbodiimide; 4-DMAP = 4-dimethylaminopyridine.

Figure 26 illustrates the olefin metathesis of precursor 164 and synthesis of epoxalones 161, 171, 170 and 172. Reagents and conditions: (a) 20 mol % of RuCl$_2$(=CHPh)(PCy$_3$)$_2$ cat., CH$_2$Cl$_2$, 25°C, 20 hours, 40% (166) plus 29% (167); (b) 20% TFA in CH$_2$Cl$_2$, 25°C, 2 hours, 89% (168), 95% (169); (c) CH$_3$CN/Na$_2$EDTA (2:1), 10.0 equivalents of CF$_3$COCH$_3$, 8.0 equivalents of NaHCO$_3$, 3.0 equivalents of Oxone®, 0°C, 34% (161) plus 15% (170), 25% (171) plus 20% (172). TFA = trifluoroacetic acid. The tentative stereochemical assignments of epoxides 161, 171, 168, 169, 170 and 172 were based on the higher potencies at 161 and 171 in the tubulin polymerization assay as compared to those of 170 and 172 respectively (see Figure 28).

Figure 27 illustrates the olefin metathesis of C6-7 diastereomeric precursor 165 and synthesis of epoxalones 175-180. Reagents and conditions. (a) 20 mol % of RuCl$_2$(=CHPh)(PCy$_3$)$_2$ cat., CH$_2$Cl$_2$, 25°C, 20 hours, 25% (173) plus 63% (174); (b) 20% TFA in CH$_2$Cl$_2$, 25°C, 2 hours, 75% (175), 72% (176) (c) CH$_3$CN/Na$_2$EDTA (2:1), 10.0 equivalents of CF$_3$COCH$_3$, 8.0

equivalents of NaHCO$_3$, 3.0 equivalents of Oxone®, 0°C, 38% (177) plus 17% (178), 22% (179) plus 13% (180).

Figure 28 illustrates the effect of epoxalones, epothilones and Taxol on tubulin polymerization. The Filtration-Colorimetric Assay was used for epothilones A and B except for the 30°C incubation temperature (instead of 37°C) and the pure tubulin (instead of microtubule protein). After initial screening of all epoxalones (161, 168, 169, 170, 171, 172, 175, 176, 177, 178, 179, and 180) at 20 mM concentrations, the most potent ones (161, 168, 169, 171 and 172) were tested together with epothilones A (1) and B and Taxol at 01, 1.0, 2.0, 3.0, 4.0 and 5.0 mM. B = epothilone B; T = Taxol.

Figure 29 illustrates the synthesis of epothilone analogs 192, 193, 194 and 195.

Figure 30 illustrates the synthesis of epothilone analogs 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, and 210.

Figure 31 illustrates the synthesis of phosphonium analog 220.

Figure 32 illustrates the synthesis of epothilone advanced intermediate macrolides 229 and 230.

Figure 33 illustrates the synthesis of epothilone analogs 233, 234, 235, and 236.

Figure 34 illustrates th synthesis of advanced int rmediate nitrile 244.

Figure 35 illustrates the synthesis of epothilone analog 249.

Figure 36 illustrates the synthesis of epothilone analog 229.

Figure 37 illustrates the synthesis of advanced intermediate aldehyde 257.

Figure 38 illustrates the synthesis of epothilone analog 263.

Figure 39 illustrates the synthesis of epothilone analog 266.

Detailed Description of the Invention

The invention is directed to epothilone analogs and methods for producing such analogs using solid and solution phase chemistries based on approaches used to synthesize epothilones A and B (Nicolaou et al. Angew. Chem. Int. Ed. Engl. 35, 2399-2401 (1996); Nicolaou et al. Angew. Chem. Int. Ed. Engl. 36, 166-168 (1997); Nicolaou et al. Angew. Chem. Int. Ed. Engl., 36, 525-527 (1997)).

The following examples illustrate meth ds for the total synthesis of epothilone A (1), epothilone B (2), designed analogs and the generation of epothilone libraries. The examples rely on the olefin metathesis reaction and macrocyclization as a means to form the macrocyclic ring. The disclosed methods promise the discovery of anticancer agents which will be superior to existing ones. The examples represent exemplary conditions which demonstrate the versatility of the methodology and are not meant to be restrictive with the models disclosed.

Example 1. Solution phase synthesis of epothilone A and B and analogs using an olefin metathesis approach (Figures 1-10)

A method using the olefin metathesis approach to synthesize epothilone A (1) and several analogs (39-41, 42-44, 51-57, 58-60, 64-65, and 67-69) is described (Figures 1-10). In this example, we describe the details of our olefin metathesis approach to epothilone A (1) and its application to the synthesis of several of its analogs. Key building blocks 6, 7 and 8 were constructed in optically active form and were coupled and elaborated to olefin metathesis precursor 4 via an aldol reaction and an esterification coupling. Olefin metathesis of compound 4, under the catalytic influence of $RuCl_2(=CHPh)(PCy_3)_2$ catalyst, furnished cis- and trans-cyclic olefins 3 and 48. Epoxidation of 49 gave epothilone A (1) and several analogs, whereas epoxidation of 50 resulted in additional epothilones. Similar elaboration of isomeric as well as simpler intermediates resulted in yet another series of epothilone analogs and model systems.

A. Retrosynthetic Analysis and Strategy (Figure 2)

The structure of epothilone A (1) is characterized by a 16-membered macrocyclic lactone carrying a cis-epoxide moiety, two hydroxyl groups, two secondary methyl groups, and a gem dimethyl group, as well as a side-chain consisting of a trisubstituted double bond and a thiazole moiety (Figure 1). With its seven stereocenters and two geometrical elements, epothilone A (1) presents a considerable challenge as a synthetic target, particularly with regard to stereochemistry and functional group sensitivity. In search for a suitable synthetic strategy, we sought to apply new principles of organic synthesis and, at the same time, retain optimum flexibility for structural diversity and construction of libraries.

In recent years, the olefin metathesis reaction became a powerful tool for organic synthesis (For the development of the olefin metathesis as a ring forming reaction, see: Zuercher et al. J. Am. Chem. Soc. 1996, 118, 6634-6640; Schwab et al. J. Am. Chem. Soc. 1996, 118, 100-110; Grubbs et al. Acc. Chem. Res. 1995, 28, 446-452; Tsuji et al. Tetrahedron Lett. 1980, 21, 2955-2959; Katz et al. Tetrahedron Lett. 1976, 4247-4250; Katz et al. Tetrahedron Lett. 1976, 4241-4254; Katz et al. J. Am. Chem. Soc. 1976, 98, 606-608; Katz et al. Advances in Organomet. Chem. 1977, 16, 283-317).

In particular, a number of publications report application of this chemistry to the construction of macrocycles (For a number of applications of the olefin metathesis reaction in medium and large ring synthesis, see: Borer et al. Tetrahedron Lett. 1994, 35, 3191-3194; Clark et al. J. Am. Chem. Soc. 1995,

117, 12364-12365; Houri et al. J. Am. Chem. Soc. 1995, 117, 2943-2944; Fürstner et al. J. Org. Chem. 1996, 61, 3942-3943; Martin et al. Tetrahedron 1996, 52, 7251-7264; Xu et al. J. Am. Chem. Soc. 1996, 118, 10926-10927).

Inspection of the structure of epothilone A (1; Figure 2) reveals the intriguing possibility of applying the olefin metathesis reaction to bis(terminal) olefin 4 to yield the cis-olefin containing macrocyclic lactone 3, which could be converted to the natural product by simple epoxidation, as retrosynthetically outlined in Figure 2. Daring as it was, this strategy has the potential of delivering both the cis- and trans-cyclic olefins corresponding to 4 for structural variation. Proceeding with the retrosynthetic analysis, an esterification reaction was identified as a means to allow disconnection of 4 to its components, carboxylic acid 5 and secondary alcohol 6. The aldol moiety in 5 allows the indicated disconnection, defining the aldehyde 7 and keto acid 8 as potential intermediates. Carboxylic acid 8 can then be traced to intermediate 9, whose asymmetric synthesis via allylboration of the known keto aldehyde 12 is straightforward. An asymmetric allylboration can also be envisioned as a means to construct alcohol 6, leading to precursor 10, which can be derived from the known thiazole derivative 11. This retrosynthetic analysis led to a highly convergent and flexible synthetic strategy, the execution of which proved to be highly rewarding in terms of delivering epothilone A (1) and a series of analogs of this naturally occurring substance for biological screening (Figure 2).

B.   <u>Construction of Key Building Blocks and Models as</u>
      <u>illustrated in Figures 3 - 6</u>

As a prelude to the total synthesis, a number of building blocks were synthesized and utilized in model studies. Thus, fragments 7, 18a, 18b and 21 (Figure 3; schemes A-C) were targeted for synthesis. Aldehyde 7 was constructed by two different routes, one of which is summarized in Figure 3A. Thus, Oppolzer's acylated sultam derivative 13 (Oppolzer et al. Tetrahedron Lett. 1989, 30, 5603-1989; Oppolzer et al. Pure & Appl. Chem. 1990, 62, 1241-1250) was alkylated with 5-iodo-1-pentene in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) to furnish compound 14 as a single diastereoisomer (by ^{1}H NMR). Lithium aluminum hydride reduction of 14 gave alcohol 15 in 60% overall yield from sultam 13. Oxidation of 15 with tetrapropylammonium perruthenate(VII) (TPAP) and 4-methyl-morpholine-N-oxide (NMO) yielded the desired aldehyde 7 in 95% yield.

The synthesis of the two antipodal alcohols 18a and 18b is outlined in Figure 3B. Thus, glycidols 16a and 16b were converted to the corresponding tert-butyldiphenylsilyl ethers (OTPS) 17a (90% yield) and 17b (94% yield), respectively, by a standard procedure (TPSCl, imidazole), and then to 18a (86% yield) and 18b (83% yield) by reaction with the vinyl cuprate reagent derived from copper(I) cyanide and vinyllithium.

Figure 3C summarizes the synthesis of the third required building block keto acid 21, starting with the known and readily available keto aldehyde 12 (Inuka et al. J. Org. Chem. 1967, 32,

404-407). Condensation of 12 with the sodium salt of phosphonate 19 produced α,β-unsaturated ester 20 in 99% yield. Cleavage of the tert-butyl ester with CF_3COOH in Methylene chloride resulted in a 99% yield of carboxylic acid 21.

With the requisite fragments in hand, we turned our attention to a feasibility study of the olefin metathesis strategy. Figure 4 summarizes the results of our work in this area. Thus, coupling of fragments 18a and 21, mediated by the action of EDC and 4-DMAP, led to ester 22a in 86% yield. Aldol condensation of the lithium enolate of keto ester 22a (generated by the action of LDA) and aldehyde 7 resulted in the formation of aldols 23 and 24 in ca. 4:3 ratio. Chromatographic separation allowed the isolation of pure 23 (42% yield) and 24 (33% yield). The stereochemical assignments of compounds 23 and 24 were based on an X-ray crystallographic analysis of a subsequent intermediate as will be described below. In Figure 4, exposure of 23 to the $RuCl_2(=CHPh)(PCy_3)_2$ catalyst in Methylene chloride solution under high-dilution conditions at 25°C for 12 hours resulted in clean formation of a single trans-macrocyclic olefin (25) ($J_{12,13}$ = 15.5 Hz) in 85% yield. Similar treatment of 24 generated the diastereomeric trans-olefin 26 ($J_{12,13}$ = 15.2 Hz) as the sole product in 79% yield. Desilylation of 25 and 26 with TBAF and AcOH in THF at 25°C gave dihydroxy lactones 27 (92% yield) and 28 (95% yield, mp 128-129°C, EtOAc-hexanes), respectively.

X-ray crystallographic analysis of macrocyclic diol 28 revealed the trans nature of the double bond and defined the

stereochemistry f all stere genic c nters. Comparison of the ^1H NMR spectra of 26 and 28 with those of 25 ($J_{12,13}$ = 15.5 Hz), 27, 31 (J12,13 = 15.7 Hz) and 32 (vide infra) supported the trans geometry of the double bond generated by the olefin metathesis, and the C6-C7 stereochemistry. Therefore, the original assignment (Nicolaou et al. Angew. Chem. Int. Ed. Engl. 1996, 35, 2399-2401) of the cis geometry for this double bond and the C6-C7 stereochemistry of the aldol products in these model systems should now be revised as shown. Ironically, it was this erroneous, but encouraging assignment that let us to embark on the final plan to synthesize epothilone A by the olefin metathesis approach. As events unfolded (vide infra), the real system produced both the cis- and the trans-cyclic olefins and the metathesis approach turned out to be fruitful.

For the purposes of analog synthesis, the 15R fragment 18b was utilized in these studies as well, as shown in Figure 5. Coupling of 18b and 21 with DCC and 4-DMAP led to a 95% yield of ester 22b, the enantiomer of 22a. LDA-mediated aldol condensation of 22b with aldehyde 7 furnished aldols 29 (54% yield) and 30 (24% yield), which are diastereomeric with 23 and 24 of Figure 4. Olefin metathesis of 29 and 30 with the $RuCl_2$(=CHPh)(PCy_3)$_2$ catalyst led to cyclic systems 31 ($J_{12,13}$ = 15.7 Hz) (80% yield) and 32 ($J_{12,13}$ = 15.4 Hz) (81% yield), respectively. Compounds 27, 28, 31 and 32 may serve as suitable precursors for the construction of a series of designed epothilones for biological investigations. At this juncture, however, it was considered more urgent to investigate the compatibility of the thiazole side-chain with the conditions of

olefin metathesis and epoxidation.

To this end, the chemistry shown in Figure 6 was studied. The enolate of keto acid 21 (2.3 equivalents of LDA, THF, $-78°C$) reacted with aldehyde 7 to afford hydroxy acids 33 and 34 as a mixture of C6-C7 (ca 2:3 by ^{1}H NMR) in good yield. This mixture was coupled with alcohol 6 in the presence of EDC and 4-DMAP, to afford two diastereomeric esters, 35 and 36 (29% and 44% yield, respectively, for two steps). Both products, 35 and 36 were subjected to the olefin metathesis reaction, and we were delighted to observe a smooth ring closure leading to trans-macrocycles 37 ($J_{12,13} = 15.5$ Hz) (86%) and 38 ($J_{12,13} = 15.0$ Hz) (66%). With cyclized product 37 and 38 in hand, we then proceeded to demonstrate the feasibility of epoxidizing the C12-C13 double bond in the presence of the sulfur and olefin functionalities in the thiazole side chain. Thus, treatment of both 37 and 38 with 0.9-1.2 equivalents of mCPBA in CHCl$_3$ at 0°C resulted in the formation of epoxides 39 (or 40) (40%), 40 (or 39) (25%, stereochemistry unassigned), and 41 (18%, stereochemistry unassigned), as well as 42 (or 43) (22%), 43 (or 42) (11%) and 44 (7%) along with some unidentified side products. These results paved the way for the final drive towards epothilone A (1). More recently we found that methyl(trifluoromethyl)dioxirane (Yang et al. J. Org. Chem. 1995, 60, 3887-3889) gives superior results in the epoxidation reactions in regard to regioselectivity and yields. Thus, olefins 37 and 38 were converted to epoxides 39 (or 40) (45%) and 40 (or 39) (28%), and epoxides 42 (or 43) (60%) and 43 (or 42) (15%), respectively. No side-chain epoxidation was observed in

either case.

C. Total Synthesis of Epothilone A and Analogs

Encouraged by the results of the model studies described above, we proceeded to assemble epothilone A (1). Figure 7 shows the initial stages of the construction beyond the key building blocks 6-8. Thus, aldol condensation of 8 (2.3 equivalents of LDA) with aldehyde 7 afforded diastereomeric products 45 and 46 (ca 3:2 ratio by ^{1}H NMR), which were coupled as a mixture with allylic alcohol 6 in the presence of EDC and 4-DMAP, to afford, after chromatographic purification, pure esters 4 (52% overall from 8) and 43 (31% overall from 8).

The olefin metathesis reaction of 4 (6R,7S stereochemistry as proven by conversion to epothilone A) proceeded smoothly in the presence of the RuCl$_2$(=CHPh)(PCy$_3$)$_2$ catalyst, as shown in Figure 8, to afford cyclic systems 8 ($J_{12,13}$ = 10.5 Hz) (46%) and 48 ($J_{12,13}$ = 15.0 Hz) (39%). The silyl ethers from 3 and 48 were removed by exposure to CF$_3$COOH in Methylene chloride, affording dihydroxy compounds 49 (90% yield) and 50 (92% yield), respectively.

The cis-olefin 49 was converted to epothilone A (1) by the action of mCPBA (0.8-1.2 equivalents) in a reaction that, in addition to 1 (35% yield), produced the isomeric epoxides 51 (13% yield), 52 (or 53) (9% yield, stereochemistry unassigned) and 53 (or 52) (7% yield, stereochemistry unassigned), as well as bis(epoxides) 54 (or 55) and 55 (or 54) (10% total yield, stereochemistry unassigned). Reaction of olefin 49 with excess

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mCPBA (1.3-2.0 equivalents) gave a different product
distribution: 1 (15%), 51 (10%), 52 (or 53) (10%), 53 (or 52)
(8%), 54 (or 55) (8%), 55 (or 54) (7%), 56 (5%), and 57 (5%).
The action of dimethyldioxirane (Murray et al. J. Org. Chem.
1985, 50, 2847-2853) (Methylene chloride, 0°C) on 49 gave mainly
1 (50%) and 51 (15%), together with small amounts of 53 (or 54)
and 54 (or 53) (10% total yield).

However, we found that the preferred procedure for this
epoxidation was the one employing methyl(trifluoro-
methyl)dioxirane (CH$_3$CN, Na$_2$EDTA, NaHCO$_3$, Oxone®, 0°C; Yang et al.
J. Org. Chem. 1995, 60, 3887-3889), a method that furnished
epothilone A (1) in 62% yield, together with smaller amount of
its α-epoxide epimer 51 (13% yield). Chromatographically
purified synthetic epothilone A (1) exhibited identical
properties to those of an authentic sample (TLC, HPLC, [α]$_D$, IR,
^{1}H and ^{13}C NMR, and Mass spec). Further, epoxidation of pure 1
with mCPBA (0.8-1.1 equivalents) resulted in the formation of
bis(epoxides) 54 (or 55) (35%) and 55 (or 54) (32%) along with
sulfoxide 57 (6%), confirming the C12-C13 stereochemical
assignments shown in Figure 8. Under similar conditions, α-
isomeric epoxide 51 was recovered unreacted.

The trans-olefinic compound 50 gave rise to another series
of epothilones A (58-60) as shown in Figure 9. Thus, epoxidation
of 50 with 1.0 equivalent of mCPBA furnished compounds 58 (or 59)
(5%, stereochemistry unassigned), 59 (or 58) (5%, stereochemistry
unassigned) and 60 (60%, stereochemistry unassigned). Similarly,
epoxidation of 5. .th 1.0 equivalent of dimethyldioxirane ·

resulted in the formati n of 58 (or 59) (10%), 59 (or 58) (10%) and 60 (40%). Interestingly, however, the action of methyl(trifluoro-methyl)dioxirane led only to 58 (or 59) (45%) and 59 (or 58) (35%) in a much cleaner fashion.

In order to expand the epothilone A library, we utilized the 6S,7R-stereoisomer 61 (obtained from 47 by CF_3COOH-induced desilylation in 90% yield) in the olefin metathesis reaction, to afford cyclic compounds 62 ($J_{12,13}$ = 9.8 Hz) (20%) and 63 ($J_{12,13}$ = 15.0 Hz) (69%) (Figure 10). Epoxidation of the dihydroxy macrocyclic compound 62 with mCPBA (0.8-1.2 equivalents) in $CHCl_3$ at -20 to 0°C gave isomeric epoxides 64 (or 65) (25%) and 65 (or 64) (23%). Side-chain epoxide 66 was not isolated in this case. Similarly, diol 63 furnished 67 (or 68) (24%), 68 (or 67) (19%), and 69 (31%) under the same reaction conditions. The stereochemistry of epothilones 64-69 remains unassigned. Again, epoxidation of compounds 62 and 63 using methyl(trifluoromethyl)dioxirane resulted in epoxides 64 (or 65) (58%) and 65 (or 64) (29%), and in epoxides 67 (or 68) (44%) and 68 (or 67) (21%), respectively, in a cleaner fashion (Figure 10).

In example 1, we illustrate methods culminating in the total synthesis of epothilone A (1) and of analogs by an olefin metathesis approach. Furthermore, besides defining the scope and limitations of this new methodology in total synthesis, the methods provide a series of epothilone A analogs for biological investigations and further chemical explorations. The high convergence and relative simplicity of the chemistry involved in this construction make this strategy available to combinatorial

synthesis for th g neration of large libraries of these structures, as illustrated in a later example.

Example 2. Solution phase synthesis of epothilone A and B and analogs using a macrolactonization approach as illustrated in Figures 11-19.

In this example, we illustrate methods for the total synthesis of both epothilones A (1) and B (2) and of a number of analogs using our macrolactonization strategy (Nicolaou Angew. Chem. Int. Ed. Engl. 1997, 36, 525-527). The reported strategy relies on a macrolactonization approach and features selective epoxidation of the macrocycle double bond in precursors 70 and 71 (Figure 1), respectively, as well as high convergency and flexibility. Building blocks 76-79 and 82 were constructed by asymmetric processes and coupled via Wittig, aldol, and macrolactonization reactions to afford the basic skeleton of epothilones and that of several of their analogs by a relatively short route. The utilization of intermediate 81, obtained via a stereoselective Wittig reaction and its Enders coupling to SAMP hydrazone 80 (Figure 17), in combination with a stereoselective aldol reaction with the modified substrate 136 (Figure 19) improved the stereoselectivity and efficiency of the total synthesis of these new and highly potent microtubule binding antitumor agents.

A. Retrosynthetic Analysis

Figure 11 outlines the macrolactonization-based retrosynthetic analysis of epothilones A (1) and B (2). Thus, retrosynthetic removal o epoxide oxygen from 1 and 2 reveals

the corresponding Z-olefins, 70 and 71, _ s potential precursors, respectively. The second major retrosynthetic step along this route is the disconnection of the macrocyclic ring at the lactone site, leading to hydroxy acids 72 and 73 as possible key intermediates. Moving further along the retrosynthetic path, an aldol-type disconnection allows the generation of keto acid 76 as a common intermediate, and aldehydes 74 and 75 as reasonable building blocks for 72 and 73, respectively. Keto acid 76 can be envisioned to arise from an asymmetric allylboration of the corresponding aldehyde, followed by appropriate elaboration of the terminal olefin. The larger intermediates, 74 and 75, can be disconnected by two slightly different ways. The first disconnection (route a) involves a retro-Wittig type reaction accompanied by a number of functional group interchanges, leading to compounds 77, 78 and 79. The second disconnection, specifically sought for its potential to address the geometry issue of the trisubstituted double bond of epothilone B (2) (route b), involves: (i) a retro-Enders alkylation, leading to hydrazone 80 and iodide 81; and (ii) a retro-Wittig type disconnection of the latter intermediate (81) to reveal aldehyde 82 and stabilized ylide 83 as potential building segments. An asymmetric allylboration of 82 then points to Brown's chiral allylborane, and an aldehyde carrying the required thiazole moiety as potential starting points.

B. Total Synthesis

1. Construction of Building Blocks (Figures 12-13):

The strategy derived from the retrosynthetic analysis discuss.. above (Figure 1), required buildi.. ..ks 76-79, 82,

and related compounds. Their c nstructi n in optically active
form proceeded as follows. Figure 12 summarizes the synthesis of
keto acid 76 starting with the known keto aldehyde 84. Thus,
addition of (+)-Ipc$_2$B(allyl) to 84 in ether at -100°C resulted in
the formation of enantiomerically enriched alcohol 85 (74% yield,
ee >98% by Mosher ester determination). Silylation of 85 with
tert-butyldimethylsilyl triflate (TBSOTf) furnished, in 98%
yield, silyl ether 86. The conversion of terminal olefin 86 to
carboxylic acid 76 was carried out in two steps: (i) ozonolysis
in Methylene chloride at -78°C followed by exposure to Ph$_3$P to
give aldehyde 87 (90% yield); and (ii) oxidation of 87 with
NaClO$_2$ in the presence of 2-methyl-2-butene and NaH$_2$PO$_4$ in tBuOH-
H$_2$O (5:1) (93% yield).

The synthesis of the thiazole-containing fragments 82 and 79
was accomplished as shown in Figure 12. Thus, the known thiazole
derivative 88 was reduced with DIBAL (1.6 equivalents, Methylene
chloride, -78°C) to aldehyde 89 (90% yield), which reacted with
the appropiate stabilized ylide [Ph$_3$P=C(Me)CHO] in benzene at
80°C to afford the required (E)-α,β-unsaturated-aldehyde 90 in
98% yield. Addition of (+)-Ipc$_2$B(allyl) to 90 in ether/pentane
at -100°C gave allylic alcohol 91 in 96% yield (>97% ee by Mosher
ester analysis). Protection of the hydroxyl group in 91 as a TBS
ether (TBSCl, imid., DMF, 99% yield), followed by chemoselective
dihydroxylation (OsO$_4$ cat., NMO) of the terminal olefin (95%
yield) and Pb(OAc)$_4$ cleavage of the resulting diol (98% yield),
furnished aldehyde 82 via intermediate 92. Finally, NaBH$_4$
reduction of 82 (96% yield), followed by iodination (I$_2$,
imidazole, Ph$_3$P, 89% yield) and phosphonium salt formation (Ph$_3$P,

neat, Δ, 98% yield) gave the requisite fragment 79 via the intermediacy of alcohol 93 and iodide 94.

The construction of aldehyde 77 and ketone 78 proceeded from SAMP hydrazone 80 as shown in Figure 13. Thus, reaction of propionaldehyde with SAMP, furnished 80, which upon sequential treatment with LDA (THF, 0°C) and 4-iodo-1-benzyloxybutane (THF, -100 to 0°C) led to compound 95 in 92% yield and >98% de (^{1}H NMR). Cleavage of the hydrazone moiety by exposure to ozone (Methylene chloride, -78°C, 77% yield), or by treatment with MeI at 60°C followed by acidic workup (aq HCl, 86% yield), followed by NaBH$_4$ reduction of the resulting aldehyde (96), furnished alcohol 97 in 98% yield. The latter compound (97) was then silylated with TBSCl in Methylene chloride in the presence of Et$_3$N and 4-DMAP to afford silyl ether 98 in 95% yield. Cleavage of the benzyl ether in 98 by hydrogenolysis [H$_2$, Pd(OH)$_2$ cat., THF, 50 psi], gave primary alcohol 99 (95% yield), which was smoothly oxidized to the desired aldehyde 77 under Swern conditions [(COCl)$_2$, DMSO, Et$_3$N, 98% yield]. Addition of MgMgBr to 77 proceeded in 84% yield, and was followed by TPAP-NMO oxidation of the resulting secondary alcohol (100) to give the other required building block, ketone 78, in 96% yield (Figure 13).

With the appropriate building blocks at hand the convergent approach to epothilones A (1) and B (2) could now enter its second phase.

    2.   Total Synthesis of Epothilones A as illustrated in

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Figure 14

The couplings of building blocks 76, 77 and 79 and the total synthesis of epothilone A (1) and its 6S,7R-diastereoisomers (111 and 112) are shown in Figure 14. Thus, generation of the ylide from phosphonium salt 79 with sodium bis(trimethylsilyl)amide (NaHMDS), followed by reaction with aldehyde 77 resulted in the formation of the desired Z-olefin 101 ($J_{12,13}$ = 10.8 Hz, obtained from decoupling experiments) as the predominant product in 77% yield, [Z:E ca 9:1; the minor isomer (E) was removed chromatographically in subsequent steps]. Parenthetically, key intermediate 101 was also prepared by Wittig coupling of phosphonium salt 114 and aldehyde 82 in a reversal of the reacting functionalities of the two fragments as shown in Figure 15. Thus, alcohol 99 was directly converted to iodide 113 by the action of I_2, imidazole, and Ph_3P (91% yield), and then to phosphonium salt 114 by heating with Ph_3P (91% yield). Generation of the ylide from 114 with equimolar amounts of NaHMDS in THF, followed by reaction with aldehyde 82 yielded Z-olefin 101 in 69% and in ca 9:1 ratio with its E-isomer.

Returning to Figure 14, selective desilylation of the primary hydroxyl group from 101, was achieved by the action of camphorsulfonic acid (CSA) in MeOH:Methylene chloride (1:1), leading to hydroxy compound 102 in 86% yield. Oxidation of 102 to aldehyde 74 was then carried out using $SO_3 \cdot pyr.$, DMSO and Et_3N (94% yield). With the availability of 74, we were then in a position to investigate its aldol condensation with keto acid 76. It was found that the optimum conditions for this coupling reaction required generation of the dilithio derivative of 76 (1.2

equivalents) with 3.0 quivalents of lithium diisopropylamide (LDA) in THF (-78 to -40°C), followed by addition of aldehyde 74 (1.0 equivalent), resulting in the formation of a mixture of the desired product 103a and its 6S,7R-diastereoisomer 103b in ca 1:1 ratio and in high yield. Despite the lack of stereoselectivity in this reaction, the result was welcome at least with regard to the prospect it provided for the construction of the 6S,7R-diastereoisomer of epothilones A and B. This mixture was then carried through to the stage of carboxylic acids 105 and 106 (Figure 14), where it was chromatographically separated to its components. Thus, exposure of 103a/103b to excess of TBSOTf and 2,6-lutidine furnished a mixture of tetra-silylated products 104a/104b, which was then briefly treated with K_2CO_3 in $MeOH_2$ to afford, after silica gel flash or preparative layer chromatography, carboxylic acids 105 (31% overall yield from 7) and 106 (30% overall yield from 74) (105: Rf = 0.61; 39: Rf = 0.70, silica gel, 5% MeOH in Methylene chloride). The indicated stereochemistry at C7 and C6 in compounds 105 and 106 was assigned later and was based on the successful conversion of 105 to epothilone A (1) as described below.

At this stage, it was necessary to selectively remove the TBS group from the allylic hydroxyl group of 105, so as to allow macrolactonization of the seco-acid substrate (72). This goal was achieved by treatment of 38 with tetra-n-butylammonium fluoride (TBAF) in THF at 25°C, generating the desired hydroxy acid 72 in 78% yield. The key macrolactonization reaction of 72 was carried out using the Yamaguchi method (2,4,6-trichlorobenzoyl chloride, Et₃N, 4-DMAP) at 25°C, affording

compound 108 in 90% yield. Rem val of both TBS groups from 108 (CF₃COOH, Methylene chloride, 0°C) furnished diol 70 in 92% yield. Finally, treatment of 70 with methyl(trifluoromethyl)dioxirane led cleanly to epothilone A (1) (62% yield) and its α-epoxide epimer (13% yield). Synthetic epothilone A (1) was chromatographically purified (preparative thin layer chromatography, silica gel) and exhibited identical properties to those of an authentic sample (TLC, HPLC, [α]D, IR, ¹H and ¹³C NMR and HRMS).

A similar sequence was followed for the synthesis of the 6S,7R-diastereoisomers 111 and 112 of epothilone A (1) from compound 106 (Figure 14) via intermediates 107 (82% yield from 106), 109 (85% yield from 107), and 110 (95% yield from 109). Epothilone 111 was obtained as the major product, together with its α-epoxide epimer 112 (87% total yield, ca 2:1 ratio) from olefinic precursor 110 by methyl(trifluoromethyl)dioxirane epoxidation.

3. Total Synthesis of Epothilones B (Figure 16)

The first approach to epothilone B (2) was designed with th aim of delivering, not only the natural substance, but also its 12S-diastereoisomer 125 (Figure 16), which in turn required the generation of both 12Z- and 12E-olefins. To this end, the ylide generated from phosphonium salt 79 with equimolar amounts of NaHMDS in THF, was reacted with ketone 78 to afford a mixture of Z- and E-olefins 115 (ca 1:1 ratio) in 73% total yield. This mixture was carried through the sequence to the stage of carboxylic ac... 119 and 120 (see Figure 16 for det... which

were chromatographically separable. Carboxylic acid 120 (mixture of geometrical isomers) with the wrong stereochemistry at C6 and C7 (6S,7R) was abandoned at this stage, whereas the mixture of Z- and E-isomers 119 with the correct stereochemistry at C6 and C7 (6R,7S) was taken to the macrolactone stage (compounds 121 and 122) via hydroxy acid 6', by: (i) selective desilylation of the C15 hydroxyl group (TBAF, THF, 75% yield); and (ii) Yamaguchi cyclization (37% yield of 121, plus 40% of 122). Deprotection of bis(silylether) 121 by treatment with CF_3COOH in Methylene chloride afforded diol 71 in 91% yield. Finally, epoxidation of 71 with mCPBA in benzene at 3°C gave epothilone B (2), together with its α-epoxide epimer 124 in 66% total yield and ca 5:1 rati (^{1}H NMR) while the use of dimethyldioxirane, gave 2 and 124 in 75% total yield in the same ratio (ca 5 : 1 in favor of 2). Epoxidation of 71 with methyl(trifluoromethyl)dioxirane in CH_3CN at 0°C improved the yield of epothilone B (2) and its α-epimer 124 to 85%, but did not significantly change the diastereoselectivity of the reaction. Epothilone B (2) was purified by silica gel preparative layer chromatography and exhibited identical properties (TLC, HPLC, $[\alpha]_D$, IR, ^{1}H and ^{13}C NMR, and HRMS) with tnose of an authentic sample.

By the same sequence, and in similar yields, the macrocycle 122 containing the E-endocyclic double bond (Figure 16), was converted to the 12S-epimeric epothilone B 125 and its α-epoxy epimer 126 via dihydroxy macrocyclic compound 123 (epoxidation with methyl(trifluoromethyl)dioxirane).

In order to improve the efficiency of the route to

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epothilon B (2), a more stereoselective total synthesis was devised and executed as follows. Figure 17 addresses the stereoselective construction of intermediate 75 with the 12Z-geometry. Thus, condensation of the stabilized ylide 83 (obtained from 4-bromo-1-butene by: (i) phosphonium salt formation; (ii) anion formation with NaHMDS; and (iii) quenching with MeOC(O)Cl) with aldehyde 82 proceeded smoothly to afford olefinic compound 127 in 95% yield and as a single isomer. Reduction of the methyl ester in 127 with DIBAL resulted in the formation of allylic alcohol 128 (98% yield), which was deoxygenated by first reacting it with Ph_3P-CCl_4, and thence with $LiEt_3BH$, to afford the desired trisubstituted 12Z-olefin 130, via chloride 129, in 82% overall yield. The latter compound 130 was regioselectively hydroborated with 9-BBN and converted to the primary alcohol 131 (91%), which was then treated with I_2-imidazole-Ph_3P to afford iodide 81 (92% yield). This iodide was then used in an Enders alkylation reaction with SAMP hydrazone 80 to give compound 132 as a single isomer (^1H NMR) and in 70% yield. Treatment of hydrazone 132 with monoperoxyphthalic acid magnesium salt (MMPP) in MeOH:phosphate pH 7 buffer (1:1) resulted in clean conversion to nitrile 133 (80% yield), which formed aldehyde 75 (82% yield) upon exposure to DIBAL at -78°C in toluene solution.

The homogeneous aldehyde 75 was converted to epothilone B (2) by the sequence depicted in Figure 18. Thus, condensation of the dianion of 76 with 75 as before (Figure 16), produced two diastereoisomers, 117a (6R,7S stereoisomer) and 117b (6S,7R stereoisomer) in high yield, and in ca 1.3:1.0 ratio (117a:117b).

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This mixture was carried thr ugh the indicated sequence to carboxylic acids 119 (32% overall yield from 75) and 119 (28% overall yield from 75), which were separated by silica gel preparative layer or flash column chromatography and taken individually further along the sequence as described for the corresponding stereoisomeric mixtures shown in Figure 16. Thus, 119 was selectively deprotected with TBAF to afford hydroxy acid 73 (73% yield), which was then cyclized to macrolactone 121 in 77% yield by the Yamaguchi method. The conversion of 121 to epothilone B (2) and its α-epoxide epimer 119 has already been described above (Figure 16).

In an effort to improve the diastereoselectivity of the aldol condensation between C1-C6 and C7-C15 fragments, the following chemistry was explored (Figure 19). Thus, ketone 136 (prepared from ketone 87, Figure 12, by selective reduction, followed by silylation) was converted to its enolate with stoichiometric amounts of LDA and reacted with aldehyde 75 (Z-isomer), affording coupling products 137 and 138 in 85% total yield and ca 3:1 ratio, with the desired compound 137 predominating as proven by its conversion to 119 and epothilone B (2). Thus, chromatographic purification (silica gel, 20% ether in hexanes) led to 137, which was efficiently transformed to the previously synthesized intermediate 119 (Figure 18) as follows. The newly generated hydroxyl group in 137 was silylated with TBSOTf-2,6-lutidine to furnish 139 (96% yield), which was then selectively desilylated at the primary position by the mild action of camphorsulfonic acid (CSA) in MeOH-Methylene chloride, leading to 140 (85%). Finally, quential oxidation of the

primary alcohol with $(COCl)_2$-DMSO-Et_3N (95% yield) and $NaClO_2$-NaH_2PO_4 (90% yield) led to hydroxy acid 119 via aldehyde 141. The conversion of 119 to 2 has already been described above (Figure 18). This sequence represents a stereoselective and highly efficient synthesis of epothilone B (2) and opens the way for the construction of further analogs within this important family of microtubule binding agents.

The chemistry described in this example defines a concise methodology for the construction of epothilones A (1) and B (2) based on a macrolactonization strategy, and which enjoys convergency and flexibility for structural diversity. The methodology is not limited to epothilones A (1) and B (2), but can be extended to numerous intermediates and structural analogs included herein. In addition, the resultant analogs will play a crucial role in elucidating structure-activity relationships of these new substances and in determining their relevance to cancer chemotherapy. Binding assays, vida infra, have demonstrated that compounds 70, 71, 123 and 125 show binding affinities to microtubules comparable to those of epothilones A (1), B (2), and Taxol™.

Example 3: <u>Solid phase synthesis of the epothilones as illustrated in Figures 20-21.</u>

In this example, we demonstrate the first solid phase synthesis of epothilone A (1) and the total synthesis of epothilone B (2), the generation of a small epothilone library, and the identification of a synthetic epothilone that interacts

with tubulin mor potently than epothilones A (1) and B (2) and
Taxol (Figures 20-24). The solid phase construction of 1 may -
herald a new era of natural products synthesis and, together with
the solution phase synthesis of 2, paves the way for the
generation of large combinatorial libraries of these important
molecules for biological screening.

The strategy for the solid phase synthesis of epothilone A
(1) was based on the retrosynthetic analysis indicated in Figure
20 (Nicolaou et al. Angew. Chem. Int. Ed. Engl. 35, 2399-2401
(1996); Yang et al. Angew. Chem. Int. Ed. Engl. 36, 166-168
(1997)). Thus, it was anticipated that the three requisite
fragments (143-145), one on a solid support (145), would be
coupled together sequentially through an aldol reaction, an
esterification reaction, and an olefin metathesis reaction, the
latter simultaneously cyclizing and liberating the product from
the solid support (144+145+143 leads to 142 which leads to 141;
Figure 20). A simple desilylation and epoxidation reaction would
then complete the total synthesis of epothilone A (1) and
analogues thereof (141 leads to 1; Figure 20). The outlook for
obtaining two products at each of the aldol, metathesis, and
epoxidation steps was considered advantageous for the purposes of
library generation.

As illustrated in Figure 21, Merrifield resin (146) was
converted to phosphonium salt 147 in >90% yield by sequential
reaction with: (i) 1,4-butanediol-NaH-n-Bu$_4$NI catalyst; (ii)
Ph$_3$P-iodine-imidazole; and (iii) Ph$_3$P. Preferred alternative
resins, other than the Merrifield resin, employable in this

procedure include PEG-polystyrene, hydroxymethyl p lystyrene, formyl polystyrene, aminomethyl polystyrene and phenolic polystyrene.   Ylide 148 generated from 147 by the action of NaHMDS in THF:DMSO at 25°C, reacted with aldehyde 149 at 0°C to form olefinic compound 150 in >70% yield. The geometry of the double bond in 150 was tentatively assigned as Z, but its geometry was neither rigorously determined nor did it matter for our purposes.   Desilylation of 150 with HF·pyr., followed by Swern oxidation of the resulting primary alcohol furnished aldehyde 145 in high yield (>95%).   The aldol condensation of the polymer-bound aldehyde 145 with the dianion derived from keto acid 144 in the presence of $ZnCl_2$ in THF gave a mixture of diastereoisomers (ca 90% yield, ca 1:1 ratio).   Finally, introduction of the heterocyclic segment 143 onto the growing substrate was achieved by esterification, leading to the required precursor 152 in ca 80% yield.   Exposure of 152 to $RuCl_2(=CHPh)(PCy_3)_2$ catalyst (153) in Methylene chloride at 25°C released from the resin olefinic compounds 154-156 and 141 (52% total yield, 154:155:156:141 ca 3:3:1:3 as determined by HPLC). Compounds 154-156 and 141 could be separated either by HPLC or by preparative layer silica gel chromatography, and the two with the correct C6-C7 stereochemistry (e.g. 155 and 141) were desilylated by exposure to TFA to afford epothilone precursors 157 (92%) and 158 (90%), respectively.   Epoxidation of 157 and 158 with trifluoro(methyl)dioxirane then furnished epothilone A (1, 70%) and its diastereoisomer 159 (45%), respectively.   The α-epoxy isomers of 1 and 159 were also obtained in these epoxidation reactions.   Pure synthetic epothilone A (1) exhibited ide l properties (TLC, $[\alpha]_D$, ^{1}H and ^{13}C NMR, IR and HRMS) to those of an

authentic sample (Figure 21).

The solid phase synthesis of epothilone A (1) described herein represents a new concept for the total synthesis of natural products, traces a highly efficient pathway to the naturally occurring epothilones, and opens the way for the generation of large combinatorial epothilone libraries. The biological results demonstrate that more potent microtubule binding analogues than the parent epothilones can be obtained (e.g. compound 71; biological results vida infra) by chemical synthesis. Furthermore, our findings point to lipophilic substituents rather than the epoxide moiety as important elements for binding activity.

Example 4.   Total Synthesis of Epoxalones A and Epoxalone Analogs

In this example, we report the total synthesis of a novel series of designed epothilones with an oxygen instead of a sulfur atom at position 20 (see Figure 24). The name epoxalones (ep for epoxide, oxa for oxazole, one for ketone; cf epothilone: ep for epoxide, thi for thiazole, one for ketone) is proposed for this new class of compounds.

The synthesis of the epoxalone A series was based on our olefin metathesis strategy toward epothilone A (1). This highly convergent and flexible sequence led to the construction of compounds 161, 168, 169, 170, 171, 172, 175, 176, 177, 178, 179, and 180 in rapid fashion starting with building blocks 7, 8 and 163 (Figure 25). Thus, asymmetric allylboration of aldehyde 162 (obtained via the procedure by Kende et al. Tetrahedron Lett.

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1995, 36, 4741-4744) with Brown's (+)-Ipc$_2$B(allyl) in Et$_2$O-pentane at -100°C furnished compound 163 in 91% yield and >98% ee. This alcohol was esterified with the mixture of carboxylic acids 45 and 46 (ca. 5:3 ratio) obtained by aldol condensation of fragments 8 and 7 to afford compounds 164 and 165 as a ca. 5:3 mixture (82% total yield). Chromatographic separation (flash column, silica gel, 20% EtOAc in hexanes) of this mixture gave pure diastereoisomers 164 and 165.

Subjection of precursor 164 (possessing the correct C6-C7 stereochemistry) to the olefin metathesis reaction [RuCl$_2$(=CHPh)(PCy$_3$)$_2$, CH$_2$Cl$_2$, 25°C] resulted in the formation of cyclic olefins 166 (40% yield) and 167 (29% yield) which were chromatographically separated (flash column, silica gel, 20% EtOAc in hexanes, 1:1) (Figure 26). Exposure of 166 to 20% trifluoroacetic acid in CH$_2$Cl$_2$ at 25°C furnished diol 168 in 89% yield. Similar treatment of 167 led to 169 (95% yield). Epoxidation of 168 with methyl(trifluoromethyl)dioxirane furnished epoxides 161 (34% yield) and 170 (15% yield) which were separated by preparative layer chromatography (silica gel, 75% EtOAc in hexanes). Similar treatment of 169 led to epoxides 171 (25%) and 172 (20%) (As illustrated in Figure 26).

A parallel sequence starting with diastereoisomer 165 led to the 6S,7R series of epoxalones 175-180 as summarized in Figure 27.

The synthesized compounds (161, 168, 169, 170, 171, 172, 175, 176, 177, 178, 179, and 180) were tested for their tubulin

assembly pr perties using the Filtration-C l rimetric Assay (outlined vida infra) at 20 mM concentrations at 30°C and with pure tubulin. The most potent ones (161, 168, 169, 171 and 172) were then assayed at 0.1, 1.0, 2.0, 3.0, 4.0 and 5.0 mM concentrations under the same conditions leading to the plots shown in Figure 28. Thus, both epoxalones 161 and 171 were found to be more potent than Taxol in inducing tubulin polymerization, whereas compounds 168, 169 and 172 showed comparable or slighlty less potencies than Taxol. The high potency of the trans-epoxide epoxalone 171 is perhaps the most striking observation in these studies and holds true for the corresponding trans-epoxides of epothilones A and B.

Example 6.   <u>Biological Evaluation of Synthesized Compounds</u>

We have carried out microtubule assays following literature procedures and evaluated synthesized compounds for their ability to form and stabilize microtubules. Cytotoxicty studies have also been carried out in our laboratories and preliminary data is disclosed vida infra.

The synthesized epothilones were tested for their action on tubulin assembly using purified tubulin with an assay developed to amplify differences between compounds more active than Taxol. As demonstrated in Figure 22, both epothilone B (2) (EC_{50} = 4.0 ±1mM) and its progenitor 71 (EC_{50} = 3.3 ±0.2mM) were significantly more active than Taxol (EC_{50} = 15.0 ±2mM) and epothilone A (1) (EC50 = 14.0 ±0.4mM), whereas compounds 125, 158 and 123 were less effective than Taxol (Lin et al. Cancer

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Chemother. Pharmacol. 38, 136-140 (1996); Rogan et al. Science 244, 994-996 (1984)).

As shown in Figure 23, cytotoxicity experiments with 1A9, 1A9PTX10 (β-tubulin mutant), 1A9PTX22 (β-tubulin mutant) and A2780AD cell lines revealed a number of interesting results (Figure 23). Thus, despite its high potency in the tubulin assembly assay, compound 71 did not display the potent cytotoxicity of 2 against 1A9 cells, being similar to 1 and Taxol. These data suggest that while the C12-C13 epoxide is not required for the epothilone-tubulin interaction, it may play an important role in localizing the agent to its target within the cell. Like the naturally occurring epothilones 1 and 2, analogu 71 showed significant activity against the MDR line A2780AD and the altered β-tubulin-expressing cell lines 1A9PTX10 and 1A9PTX22, suggesting, perhaps, different contact points for the epothilones and Taxol with tubulin (i.e. stronger binding of epothilones around residue 364 than around 270 relative to taxoids).

Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening

The colorimetric cytotoxicity assay used was adapted from Skehan et al (*Journal of National Cancer Inst* 82:1107-1112, 19901). The procedure provides a rapid, sensitive, and inexpensive method for measuring the cellular protein content of adherent and suspension cultures in 96-well microtiter plates. The method is suitable for ordinary laboratory purposes and for very large scale applications, such as the National Cancer Institute's disease-oriented in vitro anticancer-drug discovery

screen, which requires the use of several milli n culture w lls per year.

In particular, cultures fixed with trichloroacetic acid were stained for 30 minutes with 0.4% (wt/vol) sulforhodamine B (SRB) dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid, and protein-bound dye was extracted with 10 mM unbuffered Tris base [tris (hydroxymethyl)aminomethane] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The SRB assay results were linear with the number of cells and with values for cellular protein measured by both the Lowry and Bradford assays at densities ranging from sparse subconfluence t multilayered supraconfluence. The signal-to-noise ratio at 564 nm was approximately 1.5 with 1,000 cells per well. The sensitivity of the SRB assay compared favorably with sensitivities of several fluorescence assays and was superior to those of both the Lowry and Bradford assays and to those of 20 other visible dyes.

The SRB assay provides a calorimetric end point that is nondestructive, indefinitely stable, and visible to the naked eye. It provides a sensitive measure of drug-induced cytotoxicity, is useful in quantitating clonogenicity, and is well suited to high-volume, automated drug screening. SRB fluoresces strongly with laser excitation at 488 nm and can be measured quantitatively at the single-cell level by static fluorescence cytometry (Skehan et al (*Journal of National Cancer Inst* 82:1107-1112, 19901)).

Filtration Colorimetric Assay

Microtubule protein (0.25 ml of 1 mg/ml) was placed into an assay tube and 2.5 µl of the test compound were added. The sample was mixed and incubated at 37°C for 30 minutes. Sample (150 µl) was transferred to a well in a 96-well Millipore Multiscreen Durapore hydrophilic 0.22 µm pore size filtration plate which had previously been washed with 200 µl of MEM buffer under vacuum. The well was then washed with 200 µl of MEM buffer.

To stain the trapped protein on the plate, 50 µl amido black solution [0.1% naphthol blue black (Sigma)/45% methanol/ 10% acetic acid] were added to the filter for 2 minutes; then the vacuum was reapplied. Two additions of 200 µl amido black destain solution (90% methanol/2% acetic acid) were added to remove unbound dye. The signal was quantitated by the method of Schaffner and Weissmann et al. *Anal. Biochem.*, 56: 502-514, 1973 as follows:

200 µl of elution solution (25 mM NaOH-0.05 mm EDTA-50% ethanol) were added to the well and the solution was mixed with a pipet after 5 minutes. Following a 10-minutes incubation at room temperature, 150 µl of the elution solution were transferred t the well of a 96-well plate and the absorbance was measured on a Molecular Devices Microplate Reader.

Synthetic Protocals

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous

5   conditions, unless otherwise noted. Tetrahydrofuran (THF), toluene and ethyl ether (ether) were distilled from sodium-benzophenone, and methylene chloride (Methylene chloride), from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially

10 available alumina column. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

15 Reactions were monitored by thin layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or p-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle

20 size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25, 0.50 or 1 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Brucker AMX-600 or AMX-500 instruments and

25 calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR

spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with NBA as the matrix. Melting points (mp) are uncorrected and were recorded on a Thomas Hoover Unimelt capillary melting point apparatus.

Synthesis of Sultam 14. Sodium-Mediated Alkylation of *N*-Acylsultam 13 as illustrated in Figure 3. A solution of sodium bis(trimethylsilyl)amide (NaHMDS, 236 mL, 1 M in THF, 1.05 equiv) was added over 30 min at -78 °C to a solution of *N*-acylsultam 13 (synthesized according to Oppolzer et al. Tetrahedron Lett. 1989, 30, 5603-1989; Oppolzer, W. Pure & Appl. Chem. 1990, 62, 1241-1250) (61.0 g, 0.225 mol) in THF (1.1 L, 0.2 M). After stirring the resulting sodium enolate solution at -78 °C for 1 hour, freshly distilled 5-iodo-1-pentene (58 mL, 0.45 mol, 2.0 equiv) in hexamethylphosphoramide (HMPA, 117 mL, 0.675 mol, 3.0 equiv) was added. The reaction mixture was allowed to slowly warm to 25 °C, quenched with water (1.5 L) and extracted with ether (3 x 500 mL). Drying (MgSO$_4$) and evaporation of the solvents gave crude sultam 14 (76.3 g), which was used without further purification. A pure sample of 14 was obtained by preparative thin layer chromatography (250 mm silica gel plate, 10% EtOAc in hexanes). R_f = 0.57 (silica gel, 20% EtOAc in hexanes); $[a]_{22D}$ -50.5 (c 2.00, CHCl$_3$); IR (film) nmax 2939, 1694,

1331, 1216, 1131, 540 cm^{-1}; ^{1}H NMR (500 MHz, CDC13)δ 5.79-
7.72 (m, 1 H, CH2CH=CH2), 5.00-4.90 (m, 2 H, CH2CH=CH2),
3.89 (dd, J = 7.5, 5.5 Hz, 1 H, CH2CHN), 3.50⁻ (d, J = 14.0
Hz, 1 H, CH2SO2), 3.43 (d, J = 14.0 Hz, 1 H, CH2SO2),
3.15-3.06 (m, 1 H, (C=O)CH(CH3)), 2.10-2.00 (m, 3 H),
1.96-1.84 (m, 2 H), 1.78-1.68 (m, 1 H), 1.50-1.30 (m, 6
H), 1.16 (s, 3 H, C(CH3)2), 1.15 (d, J = 7.5 Hz, 3 H,
CHCH3), 0.97 (s, 3 H, C(CH3)2); 13C NMR (125.7 MHz, CDC13)
d 176.4, 138.2, 114.5, 65.1, 53.0, 48.1, 47.6, 44.5,
39.5, 38.5, 34.7, 33,2, 32.7, 26.3, 26.0, 20.7, 19,8,
16.5; HRMS (FAB), calcd for C18H30NO3S (M + H+) 340.1946,
found 340.1942.

**Synthesis of Alcohol 15 as illustrated in Figure
3A.** (Reductive Cleavage of Sultam 14). A solution of
crude sultam 14 (76.0 g, 0.224 mol) in ether (200 mL) was
added to a stirred suspension of lithium aluminum hydride
(LAH, 9.84 g, 0.246 mol, 1.1 equiv) in ether (900 mL) at -
78 °C. The reaction mixture was stirred at -78 °C for 15
min, quenched by addition of water (9.8 mL) and warmed to
0 °C. Sequential addition of 15% aqueous sodium hydroxide
solution (9.8 mL) and water (29.4 mL) was followed by
warming the reaction mixture to 25 °C. After stirring for
5 h, the aluminum salts were removed by filtration through
celite, the filtrate was dried (MgSO4) and the solvent was
removed by distillation under atmospheric pressure.
Vaccum distillation (bp. 85 °C / 8 mm Hg) furnished pure
alcohol 15 as a colorless oil (17.1 g, 60% from sultam
14). Rf = 0.40 (silica gel, 20% EtOAc in hexanes); [a]22D

-11.1 (c 1.41, CHC13); IR (film) nmax 3344, 2956, 2927, 2873, 1641, 1460, 1033, 910, 803 cm-1; 1H NMR (500 MHz, CDC13) d 5.85-5.77 (m, 1 H, CH2CH=CH2), 5.03-4.93 (m, 2 H, CH2CH=CH2), 3.53-3.49 (dd, J = 10.5, 6.0 Hz, 1 H, CH2OH), 3.44-3.41 (dd, J = 10.5, 6.5 Hz, 1 H, CH2OH), 2.09-2.01 (m, 2 H), 1.67-1.58 (m, 1 H, HOCH2CH(CH3)) 1.51-1.34 (m, 3 H), 1.17-1.08 (m, 1 H) 0.92 (d, J = 6.5 Hz, 3 H, CH3); 13C NMR (125.7 MHz, CDC13) d 138.8, 114.2, 68.0, 35.5, 33.9, 32.5, 26.2, 16.4.

Synthesis of Aldehyde 7 as illustrated in Figure 3A. (Oxidation of Alcohol 1)5. To a solution of alcohol 15 (0.768 g, 6.0 mmol) in Methylene chloride (30 mL, 0.2 M) were added powdered 4 Å molecular sieves (1.54 g), 4-methylmorpholine N-oxide (NMO, 1.06 g, 9.0 mmol, 1.5 equiv) and tetrapropylammonium perruthenate (TPAP, 0.105 g, 0.3 mmol, 0.05 equiv) at room temperature. After stirring for 30 min the disappearance of starting material was indicated by TLC. Celite was added (1.54 g) and the suspension was filtered through silica gel and eluted with Methylene chloride. The solvent was carefully distilled off under atmospheric pressure to yield aldehyde 7 (0.721 g, 95%) as a colorless oil. Rf = 0.69 (silica gel, 20% EtOAc in hexanes); [a]22D +18.3 (c 2.35, CHC13); IR (film) nmax 2934, 1707, 1463, 1238, 912 cm-1; 1H NMR (500 MHz, CDC13) d 9.58 (d, 1 H, CHO), 5.80-5.71 (m, 1 H, CH2CH=CH2), 5.00-4.90 (m, 2 H, CH2CH=CH2), 2.36-2.27 (m, 1 H), 2.10-2.00 (m, 2 H), 1.73-1.65 (m, 1 H), 1.42-1.30 (m, 3 H), 1.06 (d, J = 7.0 Hz, 3 H, CH3); 13C NMR (125.7 MHz,

CDC13) d 204.9, 138.0, 114.7, 46.0, 33.5, 29.7, 26.0, 13.1.

Synthesis of Silyl ether 17a as illustrated in Figure 3B. (Silylation of alcohol 16a). Alcohol 16a (5.0 g, 0.068 mol; glycidol; Aldrich/Sigma) was dissolved in DMF (70 mL, 1.0 M), the solution was cooled to 0 °C and imidazole (9.2 g, 0.135 mol, 2.0 equiv) was added. After stirring for 10 min, tert-butylchlorodiphenylsilane (TPSCl, 24 mL, 0.088 mol, 1.3 equiv) was added and the reaction mixture was allowed to stir for 30 min at 0 °C and for 1 h at 25 °C. Ether (70 mL) was added, followed by saturated aqueous NaHCO$_3$ solution (70 mL). The organic phase was separated and the aqueous layer was extracted with ether (50 mL), washed with water (2 x 120 mL) and with saturated aqueous NaCl solution (120 mL). The organic extract was dried (MgSO4), filtered through celite, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, 5% EtOAc in hexanes) provided silyl ether 17a (18.9 g, 90%). Rf = 0.28 (5% EtOAc in hexanes); [a]22D -1.8 (c 1.14, CHCl3); IR (film) nmax 2957, 2930, 2857, 1471, 1427, 1111, 824, 703 cm-1; 1H NMR (500 MHz, CDCl3) d 7.72-7.67 (m, 4 H, SiC(CH3)3(C6H5)2), 7.47-7.38 (m, 6 H, SiC(CH3)3(C6H5)2), 3.86 (dd, J = 12.0, 3.0 Hz, 1 H, CH2OTPS), 3.72 (dd, J = 12.0, 4.5 Hz, 1 H, CH2OTPS), 3.16-3.12 (m, 1 H, CH2-O(epoxide)CH), 2.76 (dd, J = 5.0, 4.0, 1 H, CH2-O(epoxide)CH), 2.62 (dd, J = 5.0, 3.0, 1 H, CH2-O(epoxide)CH), 1.08 (s, 9 H, SiC(CH3)3(C6H5)2); 13C NMR

(125.7 MHz, CDCl3) d 135.5, 133.2, 129.7, 127.6, 64.2, 52.2, 44.3, 26.7, 19.1.

Synthesis of Silyl ether 17b as illustrated in Figure 3B. Silylation of alcohol 16b. Following the procedure described for the synthesis of silyl ether 17a, alcohol 16b (5.0 g, 0.068 mol; Aldrich/Sigma) in DMF (70 mL, 1.0 M) was treated with imidazole (9.2 g, 0.135 mol, 2.0 equiv) and tert-butylchlorodiphenylsilane (24 mL, 0.088 mol, 1.3 equiv) to yield silyl ether 17b (19.8 g, 94%). Rf = 0.28 (5% EtOAc in hexanes); [a]22D +2.3 (c 2.00, CHCl3); IR (film nmax 2957, 2930, 2857, 1471, 1427, 1111, 824, 703 cm-1; 1H NMR (500 MHz, CDCl3) d 7.72-7.67 (m, 4 H, SiC(CH3)3(C6H5)2), 7.47-7.38 (m, 6 H, SiC(CH3)3(C6H5)2), 3.86 (dd, J = 12.0, 3.0 Hz, 1 H, CH2OTPS), 3.72 (dd, J = 12.0, 4.5 Hz, 1 H, CH2OTPS), 3.16-3.12 (m, 1 H, CH2-O(epoxide)CH), 2.76 (dd, J = 5.0, 4.0, 1 H, CH2-O(epoxide)CH), 2.62 (dd, J = 5.0, 3.0, 1 H, CH2-O(epoxide)CH) 1.08 (s, 9 H, SiC(CH3)3(C6H5)2); 13C NMR (125.7 MHz, CDCl3) d 135.5, 133.2, 129.7, 127.6, 64.2, 52.2, 44.3, 26.7, 19.1.

Synthesis of Alcohol 18a as illustrated in Figure 3B. Opening of Epoxide 17a with Vinylcuprate. To a solution of tetravinyltin (3.02 mL, 16.6 mmol, 1.25 equiv) in THF (44 mL) was added n-butyllithium (41.5 mL, 1.6 M in hexanes, 5.0 equiv) at -78 °C and the reaction mixture was stirred for 45 min. The resulting solution of vinyllithium was transferred via cannula to a solution of azeotropically dried (2 x 5 mL toluene) copper(I) cyanide

(2.97 g, 33.2 mmol, 2.5 equiv) in THF (44 mL) at -78 °C, and the mixture was allowed to warm to -30 °C. Epoxide 17a (4.14 g, 13.3 mmol) in THF (44 mL) was transferred via cannula to this vinyl cuprate solution, and the mixture was stirred at -30 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH4Cl solution (150 mL), filtered through celite, extracted with ether (2 x 100 mL) and dried (MgSO4). After removal of the solvents under reduced pressure, flash column chromatography (silica gel, 3% EtOAc in hexanes) furnished alcohol 18a (5.01 g, 86%) as a pale yellow oil. Rf = 0.33 (silica gel, 10% EtOAc in hexanes); [a]22D -2.0 (c 2.20, CHCl3); IR (film) nmax 3071, 2930, 2858, 1428, 1111, 703 cm-1; 1H NMR (500 MHz, CDCl3) d 7.70-7.65 (m, 4 H, SiC(CH3)3(C6H5)2), 7.47-7.38 (m, 6 H, SiC(CH3)3(C6H5)2), 5.84-5.75 (m, 1 H, CH2CH=CH2), 5.11-5.04 (m, 2 H, CH2CH=CH2), 3.82-3.76 (m, 1 H, CHOH), 3.67 (dd, J = 10.5, 3.5 Hz, 1 H, CH2OTPS), 3.56 (dd, J = 10.5, 7.0 Hz, 1 H, CH2OTPS), 2.27-2.22 (m, 2 H, CH2CH=CH2), 2.17 (bs, 1 H, OH), 1.08 (s, 9 H, SiC(CH3)3(C6H5)2); 13C NMR (125.7 MHz, CDCl3) d 135.6, 135.4, 134.3, 134.3, 133.1, 129.9, 129.7, 127.8, 127.6, 117.4, 71.2, 67.3, 37.5, 26.8, 19.2; HRMS (FAB), calcd for C21H28NaO2Si (M + Na+) 363.1756, found 363.1773.

Synthesis of Alcohol 18b as illustrated in Figure 3B. Opening of Epoxide 17b with Vinylcuprate. Following the procedure described for the synthesis of alcohol 18a, epoxide 17b (1.97 g, 6.3 mmol) yielded alcohol 18b (1.78 g, 83%). Rf = 0.33 (silica gel, 10% EtOAc in hexanes);

[a]22D +2.2 (c 2.00, CHCl3); IR (film) nmax 3071, 2930, 2858, 1428, 1111, 703 cm-1; 1H NMR (500 MHz, CDCl3) d 7.70-7.65 (m, 4 H, SiC(CH3)3(C6H5)2), 7.47-7.38 (m, 6 H, SiC(CH3)3(C6H5)2), 5.84-5.75 (m, 1 H, CH2CH=CH2), 5.11-5.04 (m, 2 H, CH2CH=CH2), 3.82-3.76 (m, 1 H, CHOH), 3.67 (dd, J = 10.5, 3.5 Hz, 1 H, CH2OTPS), 3.56 (dd, J = 10.5, 7.0 Hz, 1 H, CH2OTPS), 2.27-2.22 (m, 2 H, CH2CH=CH2), 2.17 (bs, 1 H, OH), 1.08 (s, 9 H, SiC(CH3)3(C6H5)2); 13C NMR (125.7 MHz, CDCl3) d 135.6, 135.4, 134.3, 134.3, 133.1, 129.9, 129.7, 127.8, 127.6, 117.4, 71.2, 67.3, 37.5, 26.8, 19.2; HRMS (FAB), calcd for C21H28NaO2Si (M + Na+) 363.1756, found 363.1773.

Synthesis of Keto Ester 20 as illustrated in Figure 3C. Horner-Wadsworth-Emmons Reaction of Aldehyde 12 with Phosphonate 19. A solution of phosphonate 19 (23.6 g, 94 mmol, 1.2 equiv; Aldrich) in THF (100 mL) was transferred via cannula to a suspension of sodium hydride (60 % dispersion in mineral oil, 5.0 g, 125 mmol, 1.6 equiv) in THF (200 mL) at 25 °C. After stirring for 15 min, the reaction mixture was cooled to 0 °C, and a solution of aldehyde 12 (10.0 g, 78 mmol; synthesized according to Inuka, T.; Yoshizawa, R. J. Org. Chem. 1967, 32, 404-407) in THF (20 mL) was added via cannula and the ice-bath was removed. After 1 h at 25 °C, TLC indicated the disappearance of aldehyde 12. The mixture was then separated between water (320 mL) and hexanes (100 mL). The aqueous layer was extracted with hexanes (100 mL) and the combined organic layers were succesively washed with

water (200 mL) and saturated aqueous NaCl solution (200
mL). Drying (MgSO4), concentration under reduced pressure
and purification by flash column chromatography (silica
gel, 10 % EtOAc in hexanes) yielded keto ester 20 (17.4 g,
99%) as a yellow oil. Rf = 0.58 (silica gel, 20% EtOAc in
hexanes); IR (film) nmax 2977, 1714, 1645, 1318, 1297,
1158 cm-1; 1H NMR (500 MHz, CDCl3) d 6.91 (d, J = 15.5
Hz, 1 H, CH=CHCOO), 5.77 (d, J = 15.5 Hz, 1 H, CH=CHCOO),
2.47 (q, J = 7.0 Hz, 2 H, CH2CH3), 1.47 (s, 9 H, C(CH3)3),
1.25 (s, 6 H, C(CH3)2), 0.99 (t, J = 7.0 Hz, 3 H, CH2CH3);
13C NMR (125.7 MHz, CDCl3) d 211.7, 165.5, 150.3, 122.2,
80.5, 50.2, 31.2, 28.0, 23.5, 7.9; HRMS (FAB), calcd for
C13H23O3 (M + H+) 227.1647, found 227.1656.

**Synthesis of Keto Acid 21 as illustrated in Figure
3C.** Hydrolysis of Keto Ester 20. Keto ester 20 (17.4 g,
77 mmol) in Methylene chloride (39 mL, 2 M) was treated
with trifluoroacetic acid (TFA, 39 mL, 2 M) at 25 °C.
Within 30 minutes TLC indicated disappearance of the
ester. The mixture was concentrated under reduced
pressure, dissolved in saturated aqueous NaHCO3 solution
(20 mL) and washed with ether (2 x 20 mL). The aqueous
phase was then acidified to pH ~ 2 with 4 N HCl, saturated
with NaCl, and extracted with EtOAc (6 x 20 mL). The
organic layer was dried (MgSO4) and concentrated under
reduced pressure to give pure keto acid 21 (13.0 g, 99%)
as a clear oil, which solidified on standing. Rf = 0.20
(silica gel, 2% TFA in Methylene chloride); mp 56-57 °C
(EtOAc); IR (film) nmax 2979, 1712, 1647, 1300, 1201 cm-1;

1H NMR (500 MHz, CDCl3) d 7.18 (d, J = 16.0 Hz, 1 H,
CH=CHCOOH), 5.89 (d, J = 16.0 Hz, 1 H, CH=CHCOOH), 2.50
(q, J = 7.0 Hz, 2 H, CH2CH3), 1.31 (s, 6 H, C(CH3)2), 1.03
(t, J = 7.0 Hz, 3 H, CH2CH3); 13C NMR (125.7 MHz, CDCl3) d
5 211.8, 171.3, 154.3, 119.6, 50.4, 31.2, 23.2, 7.7; HRMS
(FAB), calcd for C9H14NaO3 (M + Na+) 193.0841, found
193.0846.

Synthesis of Keto Ester 22a as illustrated in
10 **Figure 4.** EDC Coupling of Alcohol 18a with Keto Acid
21. A solution of keto acid 21 (2.43 g, 14.3 mmol, 1.2
equiv), 4-(dimethylamino)pyridine (4-DMAP, 0.145 g, 1.2
mmol, 0.1 equiv) and alcohol 18a (4.048 g, 11.9 mmol, 1.0
equiv) in Methylene chloride (40 mL, 0.3 M) was cooled to
15 0 °C and then treated with 1-ethyl-(3-
dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC,
2.74 g, 14.3 mmol, 1.2 equiv). The reaction mixture was
stirred at 0 °C for 2 h and then at 25 °C for 12 h. The
solution was concentrated to dryness in vacuo, and the
20 residue was taken up in EtOAc (10 mL) and water (10 mL).
The organic layer was separated, washed with saturated
NH4Cl solution (10 mL) and water (10 mL) and dried
(MgSO4). Evaporation of the solvents followed by flash
column chromatography (silica gel, 4% EtOAc in hexanes)
25 resulted in pure keto ester 22a (5.037 g, 86%). Rf = 0.41
(silica gel, 10% EtOAc in hexanes); [a]22D -6.1 (c 1.22,
CHCl3); IR (film) nmax 3072, 2960, 2933, 2858, 1715, 1645,
1470, 1428, 1295, 1181, 1112, 704 cm-1; 1H NMR (500 MHz,
CDCl3) d 7.66-7.64 (m, 4 H, SiC(CH3)3(C6H5)2), 7.44-7.36

(m, 6 H, SiC(CH3)3(C6H5)2), 7.05 (d, 1 H, J =16.0 Hz,
CH=CHCOO), 5.86 (d, J =16.0 Hz, 1 H, CH=CHCOO), 5.79-5.70
(m, 1 H, CH2CH=CH2), 5.15-5.04 (m, 3 H, CH2CH=CH2 and
CO2CH), 3.76-3.70 (m, 2 H, CH2OTPS), 2.53-2.36 (m, 4 H),
1.29 (s, 6 H, C(CH3)2), 1.04 (s, 9 H, SiC(CH3)3(C6H5)2),
1.01 (t, J = 7.0 Hz, 3 H, CH3CH2C=O); 13C NMR (125.7 MHz,
CDCl3) d 211.4, 165.7, 151.7, 135.5, 135.4, 133.2, 129.6,
127.6, 120.6, 117.9, 73.6, 64.3, 50.4, 35.0, 31.3, 26.6,
23.6, 23.5, 19.2, 7.9; HRMS (FAB), calcd for C30H40CsO4Si
(M + Cs+) 625.1750, found 625.1765.

**Synthesis of Dienes 23 and 24 as illustrated in
Figure 4.** Aldol Condensation of Ester 22a with Aldehyde
7. A solution of keto ester 22a (1.79 g, 3.63 mmol, 1.0
equiv) in THF (15 mL) was added via cannula to a freshly
prepared solution of lithium diisopropylamide [LDA; formed
by addition of n-BuLi (2.83 mL, 1.6 M solution in hexanes,
4.58 mmol, 1.25 equiv) to a solution of diisopropylamine
(0.61 mL, 4.36 mmol, 1.2 equiv) in THF (30 mL) at -10 °C
and stirring for 30 min] at -78 °C. After 15 min the
reaction mixture was allowed to warm to -40 °C and was
stirred for 45 min. The reaction mixture was cooled to -
78 °C and a solution of aldehyde 7 (0.740 g, 5.8 mmol, 1.6
equiv) in THF (15 mL) was added dropwise. The resulting
mixture was stirred for 15 min, then warmed to -40 oC for
30 min, cooled back to -78 °C and then quenched by slow
addition of saturated aqueous NH4Cl solution (10 mL). The
reaction mixture was warmed to 25 °C, diluted with EtOAc
(10 mL) and the aqueous phase was extracted with EtOAc (3

x 10 mL). The combined organic_layers were dried (MgSO4),
concentrated under reduced pressure and subjected to flash
chromatographic purification (silica gel, 5 & 20% EtOAc in
hexanes) to afford a mixture of aldol products 23 (926 mg,
42%) and 24 (724 mg, 33%), along with unreacted starting
keto ester 22a (178 mg, 10%). 23: R_f = 0.40 (silica gel,
18% EtOAc in hexanes); $[a]22D$ -11.4 (c 1.00, CHCl3); IR
(film) nmax 3518, 2962, 2932, 2858, 1722, 1644, 1294,
1182, 1114, 989, 702 cm-1; 1H NMR (600 MHz, CDCl3) d
7.67-7.63 (m, 4 H, SiC(CH3)3(C6H5)2), 7.45-7.40 (m, 2 H,
SiC(CH3)3(C6H5)22), 7.40-7.35 (m, 4 H, SiC(CH3)3(C6H5)2),
7.03 (d, 1 H, J =15.8 Hz, CH=CHCOO), 5.92 (d, J =15.8 Hz,
1 H, CH=CHCOO), 5.84-5.76 (m, 1 H, CH2CH=CH2), 5.76-5.68
(m, 1 H, CH2CH=CH2), 5.14-5.09 (m, 1 H, CO2CH), 5.08 (d, J
= 17.2 Hz, 1 H, CH2CH=CH2), 5.04 (d, J =10.1 Hz, 1 H,
CH2CH=CH2), 4.99 (d, J =18.9 Hz, 1 H, CH2CH=CH2), 4.92 (d,
J = 10.2 Hz, 1 H, CH2CH=CH2), 3.76-3.69 (m, 2 H, CH2OTPS),
3.29 (d, J = 8.9 Hz, 1 H, CHOH(CHCH3)), 3.16 (s, 1 H,
CHOH(CHCH3)), 3.13 (qd, J =7.0, 1.8 Hz, 1 H, CH3CH(C=O)),
2.52-2.45 (m, 1 H), 2.42-2.35 (m, 1 H), 2.09-1.97 (m, 2
H), 1.76-1.68 (m, 1 H), 1.52-1.43 (m, 2 H), 1.30 (s, 3 H,
C(CH3)2), 1.30 (s, 3 H, C(CH3)2), 1.30-1.25 (m, 1 H),
1.12-1.00 (m, 1 H), 1.03 (s, 9 H, SiC(CH3)3(C6H5)2), 1.01
(d, J = 7.1 Hz, 3 H, CH3CH(C=O), 0.77 (d, J = 6.8 Hz, 3 H,
CH3CHCH2; 13C NMR (150.9 MHz, CDCl3) d 217.0, 165.2,
150.1, 138.9, 135.4, 135.4, 135.4, 133.1, 133.1, 129.6,
129.6, 127.6, 127.5, 121.5, 117.9, 114.2, 74.9, 73.8,
64.4, 51.6, 41.5, 35.5, 35.2, 34.3, 32.2, 26.8, 26.2,
23.3, 23.3, 19.4, 15.6, 10.4; HRMS (FAB), calcd for

$C_{38}H_{54}CsO_5Si$ (M + Cs+) 751.2795, found 751.2766. 24: Rf = 0.30 (silica gel, 18% EtOAc in hexanes); [a]22D -1.33 (c 0.60, CHCl3); IR (film) nmax 3521, 2962, 2932, 2858, 1722, 1644, 1294, 1182, 1113, 988, 702 cm-1; 1H NMR (600 MHz, CDCl3) d 7.68-7.63 (m, 4 H, SiPh2), 7.45-7.40 (m, 2 H, SiC(CH3)3(C6H5)2), 7.40-7.35 (m, 4 H, SiC(CH3)3(C6H5)2), 7.03 (d, 1 H, J =15.8 Hz, CH=CHCOO), 5.90 (d, J =15.8 Hz, 1 H, CH=CHCOO), 5.82-5.68 (m, 2 H, 2 x CH2CH=CH2), 5.14-5.08 (m, 1 H, CO2CH), 5.09 (d, J = 16.9 Hz, 1 H, CH2CH=CH2), 5.05 (d, J =10.1 Hz, 1 H, CH2CH=CH2), 4.99 (d, J =17.1 Hz, 1 H, CH2CH=CH2), 4.95 (d, J = 10.1 Hz, 1 H, CH2CH=CH2), 3.76-3.69 (m, 2 H, CH2OTPS), 3.44 (dd, J = 6.6, 3.9 Hz, 1 H, CHOH(CHCH3)), 3.13-3.08 (m, 1 H, CH3CH(C=O)), 2.69 (bs, 1 H, CHOH(CHCH3)), 2.53-2.47 (m, 1 H), 2.43-2.37 (m, 1 H), 2.07-1.95 (m, 2 H), 1.48-1.25 (m, 5 H), 1.31 (s, 3 H, C(CH3)2), 1.29 (s, 3 H, C(CH3)2), 1.05 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.03 (s, 9 H, SiC(CH3)3(C6H5)2), 0.92 (d, J = 6.6 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3) d 216.1, 165.2, 150.3, 138.5, 135.5, 135.4, 135.4, 133.1, 133.1, 129.6, 129.6, 127.6, 127.6, 121.4, 117.9, 114.6, 75.1, 73.8, 64.4, 51.5, 42.6, 35.5, 35.1, 33.9, 32.6, 26.8, 26.0, 23.6, 23.3, 19.4, 15.0, 12.3; HRMS (FAB), calcd for $C_{38}H_{54}CsO_5Si$ (M + Cs+) 751.2795, found 751.2771.

Synthesis of Hydroxy Lactone 25 as illustrated in Figure 4. Olefin Metathesis of Diene 23. To a solution of diene 23 (0.186 g, 0.3 mmol) in Methylene chloride (100 mL, 0.003 M) was added

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bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (RuCl2(=CHPh)(PCy3)2, 25 mg, 0.03 mol, 0.1 equiv; available from Aldrich) and the reaction mixture was allowed to stir at 25 °C for 12 h. After the completion of the reaction was established by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, 30% EtOAc in hexanes) to give trans-hydroxy lactone 25 (151 mg, 85%). Rf = 0.50 (silica gel, 30% EtOAc in hexanes); $[a]22D$ +65.9 (c 0.80, CHCl3); IR (film) nmax 3520, 2960, 2932, 2858, 1711, 1705, 1646, 1292, 1183, 1114, 982, 702, 505 cm-1; 1H NMR (500 MHz, CDCl3) d 7.69–7.64 (m, 4 H, SiC(CH3)3(C6H5)2), 7.46–7.36 (m, 6 H, SiC(CH3)3(C6H5)2), 6.78 (d, J = 15.5 Hz, 1 H, CH=CHCOO), 5.98 (d, J = 15.5 Hz, 1 H, CH=CHCOO), 5.40 (ddd, J = 15.5, 8.5, 4.0 Hz, 1 H, CH=CHCH2), 5.38 (ddd, J = 15.5, 8.5, 4.5 Hz, 1 H, CH=CHCH2), 5.22–5.16 (m, 1 H, CO2CH), 3.75 (dd, J = 10.5, 6.0 Hz, 1 H, CH2OTPS), 3.70 (dd, J = 10.5, 5.0 Hz, 1 H, CH2OTPS), 3.58 (bs, 1 H, CHOH(CHCH3)), 3.05 (qd, J = 6.5, 5.5 Hz, 1 H, CH3CH(C=O)), 2.42 (d, J = 14.0 Hz, 1 H), 2.24–2.16 (m, 2 H), 2.12–2.04 (m, 1 H), 2.03–1.94 (m, 1 H), 1.55–1.40 (m, 2 H), 1.37 (s, 3 H, C(CH3)2), 1.28–1.04 (m, 3 H), 1.20 (s, 3 H, C(CH3)2), 1.15 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.05 (s, 9 H, SiC(CH3)3(C6H5)2), 0.93 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 214.8, 164.9, 149.6, 135.5, 135.4, 133.2, 133.2, 132.7, 129.6, 129.6, 127.6, 127.6, 126.3, 122.5, 75.7, 73.2, 65.6, 52.2, 42.1, 38.2, 34.8, 33.2, 30.3, 27.2, 26.9, 23.4, 23.2, 19.4, 16.3, 14.6; HRMS (FAB), calcd for

C36H50O5CsSi (M + Cs+) 723.2482, found 723.2508.

Synthesis of Hydroxy Lactone 26 as illustrated in Figure 4. Olefin Metathesis of Diene 24. Following the procedure described above for the synthesis of hydroxy lactone 25, a solution of diene 24 (0.197 g, 0.32 mmol) in Methylene chloride (100 mL, 0.003 M) was treated with bis(tricyclohexylphosphine)benzylidine ruthenium dichloride ((RuCl2(=CHPh)(PCy3)2, 26 mg, 0.032 mol, 0.1 equiv), to produce, after flash chromatography (silica gel, 18 & 25% EtOAc in hexanes), trans-hydroxy lactone 26 (150 mg, 79%). Rf = 0.3 (silica gel, 18% EtOAc in hexanes); [a]22D -3.00 (c = 0.40, CHCl3); IR (film) nmax 3522, 2961, 2931, 2857, 1718, 1698, 1646, 1294, 1182, 1113, 702 cm-1; 1H NMR (600 MHz, CDCl3): d 7.67-7.63 (m, 4 H, SiC(CH3)3(C6H5)2), 7.45-7.41 (m, 2 H, SiC(CH3)3(C6H5)2), 7.40-7.36 (m, 4 H, SiC(CH3)3(C6H5)2), 7.07 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.86 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.30 (ddd, J = 15.2, 7.4, 4.2 Hz, 1 H, CH=CHCH2), 5.28 (ddd, J = 15.2, 7.5, 4.2 Hz, 1 H, CH=CHCH2), 5.26-5.21 (m, 1 H, CO2CH), 3.77 (dd, J = 10.7, 6.3 Hz, 1 H, CH2OTPS), 3.70 (dd, 1 H, J = 10.7, 5.2 Hz, CH2OTPS), 3.27 (d, J = 9.0, 1 H, CHOH(CHCH3)), 3.13 (q, J = 6.9 Hz, 1 H, CH3CH(C=O)), 2.87 (bs, 1 H, CHOH(CHCH3)), 2.52-2.45 (m, 1 H), 2.34-2.26 (m, 1 H), 2.15-2.08 (m, 1 H), 1.97-1.89 (m, 1 H), 1.52-1.44 (m, 1 H), 1.40-1.31 (m, 1 H), 1.31 (s, 3 H, C(CH3)2), 1.30-1.20 (m, 1 H), 1.24 (s, 3 H, C(CH3)2), 1.12-1.00 (m, 1 H), 1.04 (s, 9 H, SiC(CH3)3(C6H5)2), 1.01 (d, 3 H, J = 6.9 Hz, CH3CH(C=O)),

0.96 (d, 3 H, J = 6.6 Hz, CH3CHCH2), 0.93 (m, 1 H); 13C$^-$
NMR (150.9 MHz, CDC13) d 217.8, 165.3, 151.1, 135.5,
135.4, 133.3, 133.2, 133.1, 129.6, 129.6, 127.6, 127.6,
125.6, 121.5, 75.0, 73.4, 64.9, 51.0, 43.6, 35.6, 34.2,
32.7, 32.0, 26.9, 25.6, 25.2, 24.0, 19.4, 16.0, 7.0; HRMS
(FAB), calcd for C36H50O5CsSi (M + Cs+) 723.2482, found
723.2506.

Synthesis of Diol 27 as illustrated in Figure 4.
Desilylation of TPS Ether 25. A solution of TPS ether 25
(145 mg, 0.23 mmol) in THF (4.7 mL, 0.05 M) was treated
with glacial acetic acid (70 mL, 1.15 mmol, 5.0 equiv) and
tetrabutylammonium fluoride (TBAF, 490 mL, 1 M solution in
THF, 0.46 mmol, 2.0 equiv) at 25 °C. After stirring for
36 h, no starting material was detected by TLC and the
reaction mixture was quenched by addition of saturated
aqueous NH4Cl (10 mL). Extractions with ether (3 x 10
mL), drying (MgSO4) and concentration was followed by
flash chromatographic purification (silica gel, 50% EtOAc
in hexanes) to provide diol 27 (78 mg, 92%). Rf = 0.30
(silica gel, ether), [a]22D +144.5 (c 0.51, CHCl3); IR
(film) nmax 3440, 2933, 1706, 1646, 1293, 1183, 982 cm-1;
1H NMR (600 MHz, CDCl3) d 6.82 (d, J = 16.0 Hz, 1 H,
CH=CHCOO), 6.08 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.42
(ddd, J = 15.5, 8.0, 4.5 Hz, 1 H, CH=CHCH2), 5.40 (ddd, J
= 15.5, 8.5, 4.5 Hz, 1 H, CH=CHCH2), 5.20-5.14 (m, 1 H,
CO2CH), 3.76 (dd, J = 12.0, 4.0 Hz, 1 H, CH2OH), 3.72 (dd,
J = 12.0, 6.5 Hz, 1 H, CH2OH), 3.58 (dd, J = 5.0, 2.5 Hz,
1 H, CHOH(CHCH3)), 3.06 (qd, J = 7.0, 6.0 Hz, 1 H,

CH3CH(C=O)), 2.38-2.34 (m, 1 H), 2.28-2.20 (m, 1 H), 2.12-
2.03 (m, 1 H), 2.03-1.95 (m, 1 H), 1.55-1.42 (m, 2 H),
1.40 (s, 3 H, C(CH3)2), 1.22-1.08 (m, 2 H), 1.22 (s, 3 H,
C(CH3)2), 1.15 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.08-0.86
(m, 1 H), 0.94 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C-NMR
(125.7 MHz, CDC13) d 214.8, 165.3, 150.4, 133.0, 126.0,
122.1, 75.5, 73.7, 64.9, 52.1, 41.9, 38.0, 34.4, 33.0,
30.1, 26.9, 23.2, 22.7, 16.1, 14.6; HRMS (FAB), calcd for
C20H33O5 (M + H+) 353.2328, found 353.2319.

Synthesis of Diol 28 as illustrated in Figure 4.
Desilylation of TPS Ether 26. In accordance with the
procedure describing the desilylation of TPS ether 25, a
solution of TPS ether 26 (31 mg, 0.05 mmol) in THF (1.0
mL, 0.05 M) was treated with glacial acetic acid (15 mL,
0.25 mmol, 5.0 equiv) and tetrabutylammonium fluoride
(TBAF, 105 mL, 1 M solution in THF, 0.10 mmol, 2.0 equiv)
to yield diol 28 (17 mg, 95%) as a crystalline solid. Rf
= 0.15 (silica gel, 50% EtOAc in hexanes); mp 128-129 °C
(EtOAc-hexanes); [a]22D +45.6 (c 0.80, CHC13); IR (film)
nmax 3442, 2932, 1702, 1647, 1296, 1184, 974 cm-1; 1H NMR
(600 MHz, CDC13) d 7.14 (d, J = 16.0 Hz, 1 H, CH=CHCOO),
5.94 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.34 (ddd, J = 15.4,
7.6, 4.2 Hz, 1 H, CH=CHCH2), 5.32 (ddd, J = 15.4, 7.6, 4.2
Hz, 1 H, CH=CHCH2), 5.20-5.16 (m, 1 H, CO2CH), 3.75-3.73
(m, 2 H, CH2OH), 3.28 (dd, J = 9.0, 1.2 Hz, 1 H,
CHOH(CHCH3)), 3.13 (qd, J = 7.0, 1.2 Hz, 1 H, CH3CH(C=O)),
2.81 (bs, 1 H, CHOH(CHCH3)), 2.46-2.42 (m, 1 H), 2.36-2.30
(m, 1 H), 2.17-2.13 (m, 1 H), 1.97-1.92 (m, 1 H), 1.86

(bs, 1 H, CH2OH), 1.51-1.46 (m, 1 H), 1.40-1.22 (m, 2H),
1.33 (s, 3 H, C(CH3)2), 1.27 (s, 3 H, C(CH3)2), 1.12-0.89
(m, 2 H) 1.01 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.96 (d, J
= 6.6 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDC13) d

5   217.4, 165.8, 151.9, 133.6, 125.3, 121.2, 75.0, 74.4,
64.7, 51.0, 43.8, 35.6, 34.3, 32.7, 32.0, 25.5, 25.3,
24.0, 16.0, 9.9; HRMS (FAB), calcd for $C_{20}H_{33}O_5$ (M + H+)
353.2328, found 353.2323.

10   **Synthesis of Ester 22b as illustrated in Figure 5.**
DCC Coupling of Alcohol 18b with Keto Acid 21. To a
solution of alcohol 18b (1.000 g, 2.94 mmol, 1.0 equiv),
1,3-dicyclohexylcarbodiimide (DCC, 0.836 g, 4.06 mmol, 1.4
equiv) and 4-dimethylaminopyridine (4-DMAP, 0.496 g, 4.06

15   mmol, 1.4 equiv) in toluene (30 mL, 0.1 M) was added keto
acid 21 (0.638 g, 3.75 mmol, 1.2 equiv) at 25 °C. After
12 h the reaction was complete, as indicated by TLC. The
reaction mixture was then passed through a short plug of
silica gel, eluted with toluene and concentrated under

20   reduced pressure. The crude material was submitted to
flash column chromatography (silica gel, 5% EtOAc in
hexanes) to yield pure 22b (1.38 g, 95%). Rf = 0.50
(silica gel, 17% EtOAc in hexanes); [a]22D +7.2 (c 2.00,
CHC13); IR (film) nmax 3072, 2960, 2933, 2858, 1715, 1645,

25   1470, 1428, 1295, 1181, 1112, 704 cm-1; 1H NMR (500 MHz,
CDC13) d 7.66-7.64 (m, 4 H, SiC(CH3)3(C6H5)2), 7.44-7.36
(m, 6 H, SiC(CH3)3(C6H5)2), 7.05 (d, 1 H, J =16.0 Hz,
CH=CHCOO), 5.86 (d, J =16.0 Hz, 1 H, CH=CHCOO), 5.79-5.70
(m, 1 H, CH2CH=CH2), 5.15-5.04 (m, 3 H, CH2CH=CH2 and

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CO2CH), 3.76-3.70 (m, 2 H, CH2OTPS), 2.53-2.36 (m, 4 H), 1.29 (s, 6 H, C(CH3)2), 1.04 (s, 9 H, SiC(CH3)3(C6H5)2), 1.01 (t, J = 7.0 Hz, 3 H, CH3CH(C=O)); 13C NMR (125.7 MHz, CDCl3) d 211.4, 165.7, 151.7, 135.5, 135.4, 133.2, 129.6, 127.6, 120.6, 117.9, 73.6, 64.3, 50.4, 35.0, 31.3, 26.6, 23.6, 23.5, 19.2, 7.9; HRMS (FAB), calcd for C30H40CsO4Si (M + Cs+) 625.1750, found 625.1775.

Synthesis of dienes 29 and 30 as illustrated in Figure 5. Aldol Condensation of Ester 22b with Aldehyde 7. In accordance with the procedure described for the preparation of dienes 23 and 24, keto ester 22b (0.702 g, 1.43 mmol, 1.0 equiv) in THF (8.0 mL) was treated with lithium diisopropylamide [LDA; freshly prepared from n-butyllithium (1.12 mL, 1.6 M solution in hexanes, 1.79 mmol, 1.25 equiv) and diisopropylamine (241 mL, 1.72 mmol, 1.2 equiv) in THF (16 mL)] and aldehyde 7 (289 mg, 2.29 mmol, 1.6 equiv) in THF (3.0 mL) to afford a mixture of aldol products 29 (0.478 g, 54%) and 30 (0.210 g, 24%) and along with unreacted starting material 22b (79 mg, 11%). 29: Rf = 0.39 (silica gel, 17% EtOAc in hexanes); [a]22D -6.0 (c 0.30, CHCl3); IR (film) nmax 2962, 2931, 2858, 1722, 1698, 1294, 1182, 1114, 990, 702 cm-1; 1H NMR (600 MHz, CDCl3) d 7.66-7.62 (m, 4 H, SiPh2), 7.45-7.40 (m, 2 H, SiC(CH3)3(C6H5)2), 7.40-7.35 (m, 4 H, SiC(CH3)3(C6H5)2), 7.03 (d, 1 H, J = 16.0 Hz, CH=CHCOO), 5.90 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.84-5.76 (m, 1 H, CH2CH=CH2), 5.76-5.68 (m, 1 H, CH2CH=CH2), 5.14-5.08 (m, 1 H, CO2CH), 5.09 (d, J = 17.9 Hz, 1 H, CH2CH=CH2), 5.06 (d,

J = 10.3 Hz, 1 H, CH2CH=CH2), 4.99 (d, J =17.1 Hz, 1 H, CH2CH=CH2), 4.93 (d, J = 10.2 Hz, 1 H, CH2CH=CH2), 3.76-3.69 (m, 2 H, CH2OTPS), 3.30 (d, J = 8.8 Hz, 1 H, CHOH(CHCH3)), 3.17 (s, 1 H, CHOH(CHCH3)), 3.12 (q, J = 7.0 Hz, 1 H, CH3CH(C=O)), 2.52-2.46 (m, 1 H), 2.42-2.36 (m, 1 H), 2.09-1.98 (m, 2 H), 1.76-1.68 (m, 1 H), 1.52-1.43 (m, 2 H), 1.31 (s, 3 H, C(CH3)2), 1.29 (s, 3 H, C(CH3)2), 1.30-1.25 (m, 1 H), 1.12-1.05 (m, 1 H), 1.03 (s, 9 H, SiC(CH3)3(C6H5)2), 1.00 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.77 (d, J = 6.7 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3) d 217.0, 165.2, 150.1, 138.9, 135.4, 135.4, 135.4, 133.1, 133.1, 129.6, 129.6, 127.6, 127.6, 121.5, 117.9, 114.2, 75.0, 73.9, 64.4, 51.5, 41.6, 35.5, 35.1, 34.3, 32.2, 26.8, 26.2, 23.5, 23.2, 19.4, 15.6, 10.4; HRMS (FAB), calcd for C38H54CsO5Si (M + Cs+) 751.2795, found 751.2761. 30: Rf = 0.28 (silica gel, 17% EtOAc in hexanes); [a]22D +6.2 (c 1.00, CHCl3); IR (film) nmax 2962, 2932, 2858, 1722, 1644, 1294, 1182, 1114, 988, 702 cm-1; 1H NMR (500 MHz, CDCl3) d 7.68-7.63 (m, 4 H, SiC(CH3)3(C6H5)2), 7.45-7.40 (m, 2 H, SiC(CH3)3(C6H5)2), 7.40-7.35 (m, 4 H, SiC(CH3)3(C6H5)2), 7.03 (d, 1 H, J =16.0 Hz, CH=CHCOO), 5.92 (d, J =16.0 Hz, 1 H, CH=CHCOO), 5.83-5.68 (m, 2 H, 2 x CH2CH=CH2), 5.14-5.09 (m, 1 H, CO2CH), 5.09 (d, J = 18.5 Hz, 1 H, CH2CH=CH2), 5.04 (d, J =10.5 Hz, 1 H, CH2CH=CH2), 4.99 (d, J =17.5 Hz, 1 H, CH2CH=CH2), 4.94 (d, J = 10.0 Hz, 1 H, CH2CH=CH2), 3.77-3.69 (m, 2 H, CH2OTPS), 3.43 (dd, J = 6.5, 4.0 Hz, 1 H, CHOH(CHCH3)), 3.14-3.07 (m, 1 H, CH3CH(C=O)), 2.70 (bs, 1 H, CHOH(CHCH3)), 2.53-2.46 (m, 1 H), 2.43-2.36 (m, 1 H),

2.07-1.95 (m, 2 H), 1.48-1.00 (m, 5 H), 1.30 (s, 3 H, C(CH3)2), 1.30 (s, 3 H, C(CH3)2), 1.05 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.04 (s, 9 H, SiC(CH3)3(C6H5)2), 0.91 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 216.4, 165.4, 150.4, 138.7, 135.6, 135.5, 135.5, 133.3, 133.2, 129.7, 129.7, 127.7, 127.7, 121.4, 118.0, 114.6, 75.0, 73.8, 64.3, 51.5, 42.4, 35.4, 35.1, 33.8, 32.5, 26.7, 25.9, 23.3, 19.2, 14.8, 12.2; HRMS (FAB), calcd for C38H54CsO5Si (M + Cs+) 751.2795, found 751.2770.

Synthesis of Hydroxy Lactone 31 as illustrated in Figure 5. Olefin Metathesis of Diene 29. A solution of diene 29 (104 mg, 0.17 mmol) in Methylene chloride (25 mL, 0.007 M) was treated with bis(tricyclohexylphosphine)benzylidine ruthenium dichloride ((RuCl2(=CHPh)(PCy3)2, 14 mg, 0.017 mmol, 0.1 equiv; Aldrich), in accordance with the procedure described for the preparation of hydroxy lactone 25, to furnish, after flash column chromatography (silica gel, 5 & 17% EtOAc in hexanes), hydroxy lactone 31 (79 mg, 80%). Rf = 0.18 (silica, 20% EtOAc in hexanes); [a]22D +37.5 (c = 0.50, CHCl3); IR (film) nmax 3519, 2961, 2931, 2857, 1719, 1698, 1644, 1292, 1185, 1113 cm-1; 1H NMR (600 MHz, CDCl3): d 7.67-7.62 (m, 4 H, SiC(CH3)3(C6H5)2), 7.45-7.41 (m, 2 H, SiC(CH3)3(C6H5)2), 7.41-7.36 (m, 4 H, SiC(CH3)3(C6H5)2), 7.02 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.83 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.34 (ddd, J = 15.7, 7.4, 4.7 Hz, 1 H, CH=CHCH2), 5.32 (ddd, J = 15.7, 8.0, 3.8 Hz, 1 H, CH=CHCH2), 5.26-5.21 (m, 1 H, CO2CH), 3.74 (dd, J

= 10.8, 6.1 Hz, 1 H, CH2OTPS), 3.68 (dd, 1 H, J = 10.8, 4.8 Hz, CH2OTPS), 3.58 (bs, 1 H, CHOH(CHCH3)), 3.04 (qd, J = 6.8, 2.7 Hz, 1 H, CH3CH(C=O)), 2.49-2.41 (m, 2 H), 2.30-2.22 (m, 1 H), 2.17-2.10 (m, 1 H), 1.92-1.83 (m, 1 H),- 1.65-1.50 (m, 2 H), 1.35 (s, 3 H, C(CH3)2), 1.21 (s, 3 H, C(CH3)2), 1.30-1.00 (m, 3 H), 1.11 (d, 3 H, J = 6.7 Hz, CH3CH(C=O)), 1.03 (s, 9 H, SiC(CH3)3(C6H5)2), 0.92 (d, 3 H, J = 7.0 Hz, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3) d 216.4, 165.3, 150.7, 135.4, 135.4, 133.6, 133.2, 133.1, 129.6, 129.6, 127.6, 127.6, 125.7, 122.0, 74.3, 73.5, 65.3, 51.1, 43.0, 38.3, 34.4, 31.9, 31.4, 26.8, 26.8, 25.0, 23.6, 19.4, 15.3, 12.9; HRMS (FAB), calcd for C36H50O5CsSi (M + Cs+) 723.2482, found 723.2506.

Synthesis of Hydroxy Lactone 32 as illustrated in Figure 5. Olefin Metathesis of Diene 30. A solution of diene 30 (20 mg, 0.03 mmol) in Methylene chloride (10 mL, 0.003 M) was treated with bis(tricyclohexylphosphine)benzylidine ruthenium dichloride ((RuCl2(=CHPh)(PCy3)2, 2.5 mg, 0.003 mmol, 0.1 equiv; Aldrich), in accordance with the procedure described for the preparation of hydroxy lactone 25, to produce after preparative thin layer chromatography (250 mm silica gel plate, 10% EtOAc in hexanes) hydroxy lactone 32 (15 mg, 81%). Rf = 0.34 (silica gel, 17% EtOAc in hexanes); [a]22D -90.0 (c 0.60, CHCl3); IR (film) nmax 3524, 2960, 2931, 2856, 1722, 1698, 1294, 1185, 1113, 988, 702, 505 cm-1; 1H NMR (600 MHz, CDCl3) d 7.67-7.64 (m, 4 H, SiC(CH3)3(C6H5)2), 7.45-7.41 (m, 2 H,

SiC(CH3)3(C6H5)2), 7.40-7.36 (m, 4 H, SiC(CH3)3(C6H5)2),
6.91 (d, J = 15.8 Hz, 1 H, CH=CHCOO), 5.98 (d, J = 15.8
Hz, 1 H, CH=CHCOO), 5.36 (ddd, J = 15.4, 7.3, 4.6 Hz, 1 H,
CH=CHCH2), 5.35 (ddd, J = 15.4, 7.7, 4.1 Hz, 1 H,
CH=CHCH2), 5.22-5.16 (m, 1 H, CO2CH), 3.73 (dd, J = 10.7,
5.7 Hz, 1 H, CH2OTPS), 3.69 (dd, J = 10.7, 4.9 Hz, 1 H,
CH2OTPS), 3.14 (q, J = 6.9 Hz, 1 H, CH3CH(C=O)), 3.11 (d,
J = 9.7 Hz, 1 H, CHOH(CHCH3)), 2.95 (bs, 1 H, CHOH(CHCH3)),
2.44-2.39 (m, 1 H), 2.30-2.23 (m, 1 H), 2.16-2.11 (m, 1
H), 1.99-1.92 (m, 1 H), 1.44-1.38 (m, 2 H), 1.33 (s, 3 H,
C(CH3)2), 1.23-1.05 (m, 3 H), 1.22 (s, 3 H, C(CH3)2), 1.04
(s, 9 H, SiC(CH3)3(C6H5)2), 1.02 (d, J = 6.9 Hz, 3 H,
CH3CH(C=O)), 0.96 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR
(125.7 MHz, CDCl3) d 216.6, 164.8, 150.0, 135.5, 135.4,
133.2, 133.2, 132.9, 129.6, 129.6, 127.6, 127.6, 126.3,
122.5, 73.8, 73.3, 65.6, 52.0, 41.1, 36.0, 34.6, 33.6,
32.4, 26.9, 25.7, 22.8, 22.8, 19.4, 16.2, 10.5; HRMS
(FAB), calcd for C36H50O5CsSi (M + Cs+) 723.2482, found
723.2508.

**Synthesis of Hydroxy Acids 33 and 34 as
illustrated in Figure 6.** Aldol Condensation of Acid
21 with Aldehyde 7. A solution of keto acid 21 (752 mg,
4.42 mmol, 1.0 equiv) in THF (22 mL) was added dropwise at
-78 °C to a freshly prepared solution of LDA [formed by
addition of n-BuLi (6.49 mL, 1.6 M solution in hexanes,
10.4 mmol, 2.35 equiv) to a solution of diisopropylamine
(1.43 mL, 10.2 mmol, 2.3 equiv) in THF (44 mL) at -10 °C
and stirring for 30 min]. After stirring for 15 min the

reaction mixture was allowed to warm to -30 °C and stirred at that temperature for 1.5 h. The reaction mixture was cooled back to -78 °C and a solution of aldehyde 7 (0.891 g, 7.07 mmol, 1.6 equiv) in THF (22 mL) was added via cannula. The resulting mixture was stirred for 15 min at -78 °C, then warmed to -40 oC and stirred for 1 h, cooled to -78 °C and quenched by slow addition of saturated aqueous NH4Cl (10 mL) solution. The reaction mixture was warmed to 0 °C, and acetic acid (1.26 mL, 22.1 mmol, 5.0 equiv) was added, followed by warming to 25 °C. Extractions with EtOAc (6 x 15 mL), filtration througth a short plug of silica gel and concentration afforded, in high yield, a mixture of aldol products 33 and 34 along with unreacted starting acid 21 in a 35:50:15 ratio (1H NMR). This crude material was used without further purification. 1H NMR (500 MHz, CDCl3; only signals for 33 and 34 are reported) d 7.16 (d, J = 16.0 Hz, 1 H, CH=CHCOOH), 5.95 (d, J = 16.0 Hz, 1 H, CH=CHCOOH), 5.86-5.73 (m, 1 H, CH2CH=CH2), 5.02-4.91 (m, 2 H, CH2CH=CH2), 3.46-3.32 (m, 1 H, CHOH(CHCH3)), 3.17-3.11 (m, 1 H, CH3CH(C=O)), 2.09-1.98 (m, 2 H, CH2CH=CH2), 1.72-1.24 (m, 9 H), 1.14-1.02 (m, 5 H), 0.95-0.81 (m, 3 H); HRMS (FAB), calcd for C17H2904 (M + H+) 297.2066, found 297.2074.

Synthesis of Esters 35 and 36 as illustrated in Figure 6. EDC Coupling of Alcohol 6 with Keto Acids 33 and 34. By analogy to the procedure described above for the synthesis of est·· 22a, a solution of keto acids 33 and 34 (1.034 g cruce), 4-dimethylaminopyridine (4-DMAP,

43 mg, 0.35 mmol), and alcohol 6 (1.1 g, 5.24 mmol;
synthesized vida infra as compound 91; eg. alcohol 6 as
shown in figure 6 is the same compound as compound 91 as
shown in figure 12) in Methylene chloride (4 mL) was
treated with 1-ethyl-(3-dimethylaminopropyl)-3-
carbodiimide hydrochloride (EDC, 1.00 g, 5.24 mmol) to
provide, after column chromatography (silica gel, 20%
EtOAc in hexanes), ester 35 (0.567 g, 29% from keto acid
21) and ester 36 (0.863 g, 44% from keto acid 21). 35:
Rf = 0.27 (silica gel, 20% EtOAc in hexanes); [a]22D -7.3
(c 2.90, CHCl3); IR (film) nmax 3510, 2973, 2932, 1719,
1703, 1641, 1459, 1293, 1179, 985 cm-1; 1H NMR (500 MHz,
CDCl3) d 7.03 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.95 (s, 1
H, ArH), 6.53 (s, 1 H, ArCH=CCH3), 5.95 (d, J = 16.0 Hz, 1
H, CH=CHCOO), 5.80-5.69 (m, 2 H, 2 x CH2CH=CH2), 5.39 (t,
J = 6.5 Hz, 1 H, CO2CH), 5.10 (d, J = 17.5 Hz, 1 H,
CH2CH=CH2), 5.05 (d, J = 10.5 Hz, 1 H, CH2CH=CH2), 4.97
(d, J = 17.0 Hz, 1 H, CH2CH=CH2), 4.93 (d, J = 10.0 Hz, 1
H, CH2CH=CH2), 3.43 (dd, J = 6.5, 4.0 Hz, 1 H,
CHOH(CHCH3)), 3.11 (qd, J = 7.0, 4.0 Hz, 1 H, CH3CH(C=O)),
2.76 (bs, 1 H, CHOH(CHCH3)), 2.69 (s, 3 H, CH3Ar), 2.57-
2.47 (m, 2 H, CH2CH=CH2), 2.08 (d, J = 1.0 Hz, 3 H,
ArCH=CCH3), 2.07-1.93 (m, 2 H, CH2CH=CH2), 1.47-1.28 (m, 4
H), 1.30 (s, 3 H, C(CH3)2), 1.28 (s, 3 H, C(CH3)2), 1.05
(d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.05-0.98 (m, 1 H), 0.91
(d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3)
d 216.3, 165.0, 164.7, 152.2, 150.5, 138.6, 136.9, 133.2,
121.4, 120.8, 117.8, 116.4, 114.6, 78.4, 75.0, 51.5, 42.6,
37.5, 35.3, 33.7, 32.5, 25.9, 23.2, 23.2, 19.1, 14.8,

12.2; HRMS (FAB), calcd for C28H42NO4S (M + H+) 488.2835, found 488.2843. 36: Rf = 0.34 (silica gel, 20% EtOAc in hexanes); [a]22D -9.2 (c 1.00, CHCl3); IR (film) nmax 3519, 2930, 1716, 1641, 1457, 1293, 1179, 986 cm-1; 1H NMR (500 MHz, CDCl3) d 7.04 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.95 (s, 1 H, ArH), 6.54 (s, 1 H, ArCH=CCH3), 5.96 (d, J = 15.5 Hz, 1 H, CH=CHCOO), 5.84-5.69 (m, 2 H, 2 x CH2CH=CH2), 5.40 (t, J = 6.5 Hz, 1 H, CO2CH), 5.10 (d, J = 17.0 Hz, 1 H, CH2CH=CH2), 5.05 (d, J = 10.5 Hz, 1 H, CH2CH=CH2), 4.98 (d, J = 17.5 Hz, 1 H, CH2CH=CH2), 4.92 (d, J = 9.0 Hz, 1 H, CH2CH=CH2), 3.30 (dd, J = 8.5, 1.5 Hz, 1 H, CHOH(CHCH3)), 3.13 (qd, J = 7.0, 2.0 Hz, 1 H, CH3CH(C=O)), 2.70 (s, 3 H, CH3Ar), 2.57-2.49 (m, 2 H, CH2CH=CH2), 2.09 (s, 3 H, ArCH=CCH3), 2.09-1.96 (m, 2 H, CH2CH=CH2), 1.74-1.68 (m, 1 H), 1.52-1.43 (m, 2 H), 1.32 (s, 3 H, C(CH3)2), 1.30 (s, 3 H, C(CH3)2), 1.30-1.01 (m, 2 H), 1.02 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.79 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 217.3, 165.1, 164.7, 152.4, 150.4, 139.0, 136.8, 133.2, 121.6, 121.0, 117.8, 116.4, 114.3, 78.5, 74.9, 51.5, 41.5, 37.5, 35.4, 34.1, 32.1, 26.0, 23.2, 23.0, 19.2, 15.5, 14.7, 10.2; HRMS (FAB), calcd for C28H44CsNO4S (M + Cs+) 620.1811, found 620.1838.

Synthesis of Hydroxy Lactone 37 as illustrated in Figure 6. Olefin Metathesis of Diene 35. A solution of diene 35 (58 mg, 0.12 mmol) in Methylene chloride (129 mL, 0.001 M) was treated with bis(tricyclohexylphosphine)benzylidine ruthenium

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dichloride ((RuCl2(=CHPh)(PCy3)2, 10 mg, 0.0012 mmol, 0.1 equiv; Aldrich), in accordance with the procedure described for the synthesis of hydroxy lactone 25, to furnish, after column chromatography (silica gel, 15% EtOAc in hexanes) hydroxy lactone 37 (48 mg, 86%). Rf = 0.63 (silica gel, 33% EtOAc in hexanes); $[a]22D$ -14.8 (c 1.90, CHCl3); IR (film) nmax 3510, 2931, 1709, 1646, 1458, 1295, 1178, 976, 732 cm-1; 1H NMR (500 MHz, CDCl3) d 7.15 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.96 (s, 1 H, ArH), 6.58 (s, 1 H, ArCH=CCH3), 5.95 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.56 (dd, J = 9.5, 3.0 Hz, 1 H, CO2CH), 5.36 (ddd, J = 15.5, 7.3, 3.5 Hz, 1 H, CH=CHCH2), 5.35 (ddd, J = 15.5, 7.3, 3.5 Hz, 1 H, CH=CHCH2), 3.33 (d, J = 9.0 Hz, 1 H, CHOH(CHCH3)), 3.16 (q, J = 7.0 Hz, 1 H, CH3CH(C=O)), 2.88 (bs, 1 H, CHOH(CHCH3)), 2.71 (s, 3 H, CH3Ar), 2.56-2.42 (m, 2 H, CH=CHCH2), 2.18-2.06 (m, 1 H, CH=CHCH2), 2.10 (s, 3 H, ArCH=CCH3), 1.99-1.90 (m, 1 H, CH=CHCH2), 1.52-1.20 (m, 3 H), 1.31 (s, 3 H, C(CH3)2), 1.28 (s, 3 H, C(CH3)2), 1.17-0.90 (m, 2 H), 1.02 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.97 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 217.8, 165.1, 164.8, 152.1, 151.5, 138.3, 133.4, 125.8, 121.5, 119.3, 116.0, 76.8, 74.9, 50.8, 43.7, 36.7, 35.5, 32.5, 31.8, 25.4, 25.2, 23.9, 19.0, 15.8, 15.5, 9.7; HRMS (FAB), calcd for C26H37CsNO4S (M + Cs+) 592.1498, found 592.1516.

Synthesis of Hydroxy Lactone 38 as illustrated in Figure 6. Olefin Metathesis of Diene 36. A solution of diene 36 (167 mg, 0.34 mmol) in Methylene chloride (340

mL, 0.001 M) was treated with bis(tricyclohexylphosphine)benzylidine ruthenium dichloride ((RuCl2(=CHPh)(PCy3)2, 28 mg, 0.034 mmol, 0.1 equiv; Aldrich), in accordance with the procedure described for the synthesis of hydroxy lactone 25, to furnish, after column chromatography (silica gel, 20% EtOAc in hexanes) hydroxy lactone 38 (103 mg, 66%). Rf = 0.38 (silica gel, 30% EtOAc in hexanes); [a]22D +70.4 (c 1.60, CHCl3); IR (film) nmax 2933, 1703, 1640, 1292, 1179, 982 cm-1; 1H NMR (500 MHz, CDCl3) d 6.99 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 6.55 (s, 1 H, ArCH=CCH3), 6.02 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.51 (dd, J = 8.0, 2.5 Hz, 1 H, CO2CH), 5.47 (ddd, J = 15.0, 7.5, 7.5 Hz, 1 H, CH=CHCH2), 5.38 (ddd, J = 15.0, 7.5, 7.5 Hz, 1 H, CH=CHCH2), 3.60 (d, J = 6.8 Hz, 1 H, CHOH(CHCH3)), 3.14 (dq, J = 7.0, 7.0 Hz, 1 H, CH3CH(C=O)), 2.70 (s, 3 H, CH3Ar), 2.48-2.37 (m, 2 H, CH=CHCH2), 2.21-2.12 (m, 1 H, CH=CHCH2), 2.08 (s, 3 H, ArCH=CCH3), 1.98-1.90 (m, 1 H, CH=CHCH2), 1.62-1.52 (m, 1 H), 1.41-1.32 (m, 2H), 1.36 (s, 3 H, C(CH3)2), 1.21 (s, 3 H, C(CH3)2), 1.17-1.07 (m, 1H), 1.14 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.98-0.87 (m, 1H), 0.97 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 215.5, 165.0, 164.6, 152.2, 150.9, 137.4, 133.6, 126.0, 121.9, 119.4, 115.6, 76.6, 76.2, 51.6, 44.1, 37.9, 36.2, 33.3, 29.6, 27.1, 24.0, 23.0, 18.9, 17.0, 15.9, 15.4; HRMS (FAB), calcd for C26H38NO4S (M + H+) 460.2522, found 460.2534.

Synthesis of Epothilones 39, 40 and 41 as

illustrated in Figure 6. Epoxidation of trans-Hydroxy
Lactone 37. Procedure A: A solution of trans-hydroxy
lactone 37 (20 mg, 0.06 mmol) in CHCl3 (1 mL, 0.06 M) was
treated with meta-chloroperbenzoic acid (mCPBA, 57-86 %,
15 mg, 0.05-0.07 mol, 0.9-1.2 equiv) at -20 °C, and the
reaction mixture was allowed to warm up to 0 oC. After 12
h, disappearance of starting material was detected by TLC,
and the reaction mixture was then washed with saturated
aqueous NaHCO3 solution (2 mL) and the aqueous phase was
extracted with EtOAc (3 x 2 mL). The combined organic
layer was dried (MgSO4), filtered and concentrated.
Purification by preparative thin layer chromatography (250
mm silica gel plate, 30% EtOAc in hexanes) furnished
epothilones 39 (or 40) (12 mg, 40%), 40 (or 39) (7.5 mg,
25%) and 41 (5.4 mg, 18%). Procedure B: To a solution of
trans-hydroxy lactone 37 (32 mg, 0.07 mmol) in
acetonitrile (1.0 mL) was added a 0.0004 M aqueous
solution of disodium salt of ethylenediaminetetraacetic
acid (Na2EDTA, 0.5 mL) and the reaction mixture was cooled
to 0 °C. Excess of 1,1,1-trifluoroacetone (0.2 mL) was
added, followed by a portionwise addition of Oxone® (200
mg, 0.35 mmol, 5.0 equiv) and NaHCO3 (50 mg, 0.56 mmol,
8.0 equiv) with stirring, until the disappearance of
starting material was detected by TLC. The reaction
mixture was then treated with excess dimethyl sulfide (150
mL) and water (1.0 mL) and then extracted with EtOAc (4 x
2 mL). The combined organic layer was dried (MgSO4),
filtered, and concentrated. Purification by preparative
thin layer chromatography (250 mm silica gel plate, 70%

EtOAc in hexanes) provided a mixture of diastereomeric epoxides, epoxide 39 (or 40) (15 mg, 45%) and a-isomeric epoxide 40 (or 39) (9.2 mg, 28%). 39 (or 40): Rf = 0.23 (silica gel, 33% EtOAc in hexanes); $[a]22D$ -23.7 (c 0.30, CHC13); IR (film) nmax 3500, 2970, 2930, 2859, 1714, 1696, 1651, 1643, 1634, 1293, 1176, 991 cm-1; 1H NMR (600 MHz, CDC13) d 7.18 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=CCH3), 5.94 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.71 (d, J = 11.1 Hz, 1 H, CO2CH), 3.52 (d, J = 6.0 Hz, 1 H, CHOH(CHCH3)), 3.07 (q, J = 6.9 Hz, 1 H, CH3CH(C=O)), 2.76 (d, J = 8.0 Hz, 1 H), 2.70 (s, 3 H, CH3Ar), 2.61 (bs, 2 H), 2.29 (d, J = 14.5 Hz, 1 H), 2.09 (s, 3 H, ArCH=CCH3), 1.82-1.76 (m, 1 H), 1.75-1.68 (m, 1 H), 1.60-0.98 (m, 6 H), 1.35 (s, 3 H, C(CH3)2), 1.29 (s, 3 H, C(CH3)2), 1.11 (d, J = 6.9 Hz, 3 H, CH3CH(C=O)), 1.01 (d, J = 6.7 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDC13) d 216.4, 165.1, 164.7, 152.0, 151.9, 136.7, 121.3, 120.5, 116.6, 76.3, 72.3, 59.3, 56.6, 51.1, 45.2, 36.7, 36.7, 33.3, 32.2, 25.3, 23.5, 22.4, 19.4, 15.5, 15.1, 10.9; HRMS (FAB), calcd for C26H37NO5S (M + H+) 608.1447, found 608.1469; 40 (or 39): Rf = 0.26 (silica gel, 33% EtOAc in hexanes); $[a]22D$ -20.0 (c 0.25, CHC13); IR (film) nmax 3517, 2927, 2856, 1715, 1698, 1644, 1293, 1176, 989 cm-1; 1H NMR (500 MHz, CDC13) d 7.26 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=CCH3), 5.98 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.50 (d, J = 6.5 Hz, 1 H, CO2CH), 3.47 (d, J = 8.0 Hz, 1 H, CHOH(CHCH3)), 3.19 (q, J = 7.0 Hz, 1 H, CH3CH(C=O)), 2.78 (t, J = 6.5 Hz, 2 H), 2.71 (s, 3 H, CH3Ar), 2.32-2.26 (m, 1 H), 2.11 (s, 3

H, ArCH=CCH3), 1.91-1.86 (m, 1 H), 1.76-1.17 (m, 7 H), 1.36 (s, 3 H, C(CH3)2), 1.30 (s, 3 H, (C(CH3)2), 1.08 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.98 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 216.9, 165.0, 164.6, 152.0, 151.4, 136.6, 121.7, 119.6, 116.3, 76.1, 73.6, 57.3, 54.1, 51.2, 44.1, 35.3, 35.0, 32.8, 30.8, 24.3, 23.6, 21.9, 19.3, 16.1, 15.5, 10.7; HRMS (FAB), calcd for C26H38CsNO5S (M + Cs+) 608.1447, found 608.1469.

41: Rf = 0.43 (silica gel, 33% EtOAc in hexanes); [a]22D -14.0 (c 0.10, CHCl3); IR (film) nmax 3482, 2925, 1722, 1642, 1176cm-1; 1H NMR (500 MHz, CDCl3) d 7.14 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.97 (s, 1 H, ArH), 5.92 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.35-5.33 (m, 2 H, CH=CHCH2), 5.13 (dd, J = 10.5, 3.0 Hz, 1 H, CO2CH), 4.20 (s, 1 H, ArCH-O(epoxide)CCH3), 3.30 (d, J = 9.0 Hz, 1 H, CHOH(CHCH3)), 3.13 (q, J = 7.5 Hz, 1 H, CH3CH(C=O)), 2.76 (d, J = 2.0 Hz, 1 H), 2.72 (s, 3 H, CH3Ar), 2.58 (dd, J = 14.1, 2.4 Hz, 1 H), 2.46-2.40 (m, 1 H), 2.22-2.16 (m, 1 H), 2.02-1.87 (m, 2 H) 1.68- 0.82 (m, 3 H), 1.31 (s, 3 H, C(CH3)2), 1.28 (s, 3 H, C(CH3)2), 1.25 (s, 3 H, ArCH-O(epoxide)CCH3), 1.01 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.97 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 217.5, 166.3, 165.1, 152.1, 150.9, 133.8, 125.4, 121.0, 115.5, 75.1, 74.2, 59.5, 51.0, 44.0, 35.7, 34.1, 32.7, 32.0, 29.8, 25.6, 25.5, 24.1, 19.3, 16.0, 13.0, 9.8; HRMS (FAB), calcd for C26H37CsNO5S (M + Cs+) 608.1447, found 608.1423.

Synthesis of Epothilones 42, 43 and 44 af

illustrated in Figure 6. Epoxidation of trans-Hydroxy
Lactone 38. Procedure A: A solution of trans-hydroxy
lactone 38 (32 mg, 0.07 mmol) in CHCl3 (1.4 mL) was
reacted with meta-chloroperbenzoic acid (mCPBA, 57-86%,

5   17.8 mg, 0.06-0.09 mmol, 0.9=1.3 equiv), according to
procedure A described for the epoxidation of 37, resulting
in the isolation of epoxides 42 (or 43) (7.3 mg, 22%), 43
(or 42) (3.7 mg, 11%), and 44 (2.2 mg, 7%)
(stereochemistry unassigned for all compounds), along with

10   unreacted starting material (3.5 mg, 11%), after two
consecutive preparative thin layer chromatographic
purifications (250 mm silica gel plate, ether). Procedure
B: As described in procedure B for the epoxidation of
trans-hydroxy lactone 37, cis-hydroxy lactone 38 (24 mg,

15   0.05 mmol) in MeCN (800 mL) was treated with a 0.0004 M
aqueous solution of disodium salt of
ethylenediaminetetraacetic acid (Na2EDTA, 380 mL), 1,1,1-
trifluoroacetone (150 mL), Oxone® (144 mg, 0.25 mmol, 5.0
equiv) and NaHCO3 (36 mg, 0.40 mmol, 8.0 equiv), to yield,

20   after purification by preparative thin layer
chromatography (250 mm silica gel plate, ether), epoxides
42 (or 43) (15 mg, 60%), 43 (or 42) (3.8 mg, 15%). 42 (or
43): Rf = 0.60 (silica gel, ether); [a]22D +78.5 (c 0.94,
CHCl3); IR (film) nmax 3500, 2929, 1714, 1644, 1462, 1293,

25   1179, 982 cm-1; 1H NMR (500 MHz, CDCl3) d 6.98 (s, 1 H,
ArH), 6.89 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 6.58 (s, 1 H,
ArCH=CCH3), 6.06 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.69 (d,
J = 11.0 Hz, 1 H, CO2CH), 3.80-3.73 (m, 1 H, CHOH(CHCH3)),
3.11 (dq, J = 7.0, 7.0 Hz, 1 H, CH3CH(C=O)), 2.82-2.74 (1 ,

2 H), 2.71 (s, 3 H, CH3Ar), 2.43 (d, J = 14.5 Hz, 1 H), 2.11-(s, 3 H, ArCH=CCH3), 1.93-1.85 (m, 1 H), 1.60-0.98 (m, 7 H), 1.46 (s, 3 H, C(CH3)2), 1.24 (s, 3 H, C(CH3)2), 1.14 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.01 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDC13) d 212.7, 165.0, 164.7, 152.0, 151.7, 137.0, 121.1, 120.6, 116.7, 76.2, 75.7, 58.7, 57.7, 52.2, 44.4, 37.3, 36.1, 33.5, 30.0, 24.2, 23.0, 22.1, 19.3, 18.1, 14.9, 14.5; HRMS (FAB), calcd for C26H37NO5S (M + H+) 476.2471, found 476.2485. 43 (or 42): Rf = 0.64 (silica gel, ether); [a]22D +38.0 (c 0.20, CHC13); IR (film) nmax 3479, 2926, 2855, 1721, 1702, 1643, 1455, 1174 cm-1; 1H NMR (500 MHz, CDC13) d 7.08 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 7.01 (s, 1 H, ArH), 6.63 (s, 1 H, ArCH=CCH3), 6.05 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.47 (dd, J = 7.6, 2.6 Hz, 1 H, CO2CH), 3.65 (dd, J = 6.5, 3.5 Hz, 1 H, CHOH(CHCH3)), 3.19 (dq, J = 6.8, 6.8 Hz, 1 H, CH3CH(C=O)), 2.85-2.80 (m, 1 H), 2.78-2.72 (m, 1 H), 2.73 (s, 3 H, CH3Ar), 2.52 (ddd, J = 15.0, 8.5, 4.0 Hz, 1 H), 2.10 (s, 3 H, ArCH=CCH3), 1.73 (ddd, J = 15.0, 7.5, 3.5 Hz, 1 H), 1.65-0.80 (m, 7 H), 1.43 (s, 3 H, C(CH3)2), 1.26 (s, 3 H, C(CH3)2), 1.15 (d, J = 6.8 Hz, 3 H, CH3CH(C=O)), 0.99 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDC13) d 215.1, 165.5, 164.7, 152.1, 152.0, 130.9, 128.8, 120.9, 115.9, 75.7, 75.2, 57.6, 55.6, 51.7, 44.3, 37.5, 34.4, 32.3, 31.1, 23.9, 23.3, 22.8, 18.8, 17.2, 15.8, 14.6; HRMS (FAB), calcd for C26H37NO5S (M + H+) 476.2471, found 476.2489. 44: Rf = 0.60 (silica gel, ether); [a]22D +23.3 (c 0.06, CHC13); IR (film) nmax 3443, 2924, 1731, 1462, 1260 cm-1; 1H NMR (500 MHz, CDC13)

d 6.97 (s, 1 H, ArH), 6.84 (d, J = 16.0 Hz, 1 H,
CH=CHCOO), 6.04 (d, J = 16.0 Hz, 1 H, CH=CHCOO), 5.51-5.43
(m, 1H, CH=CHCH2), 5.42-5.35 (m, 1H, CH=CHCH2), 5.05 (dd,
J = 10.0, 2.5 Hz, 1 H, CO2CH), 4.18 (s, 1H, ArCH-
O(epoxide)CCH3), 3.60-3.57 (m, 1 H, CHOH(CHCH3)), 3.06
(dq, J = 7.0, 7.0 Hz, 1 H, CH3CH(C=O)), 2.72 (s, 3 H,
CH3Ar), 2.56-2.50 (m, 1 H), 2.40-2.32 (m, 1 H), 2.30-2.22
(m, 1 H), 2.14-1.96 (m, 2 H), 1.60-0.98 (m, 4 H), 1.38 (s,
3H, ArCH-O(epoxide)CCH3), 1.30 (s, 3 H, C(CH3)2), 1.22 (s,
3 H, C(CH3)2), 1.14 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.95
(d, J = 7.0 Hz, 3 H, CH3CHCH2); HRMS (FAB), calcd for
$C_{26}H_{38}NO_5S$ (M + H+) 476.2471, found 476.2492.

**Synthesis of Hydroxy Keto Acids 45 and 46 as
illustrated in Figure 7.** Aldol Condensation of Keto
Acid 8 and Aldehyde 7. In accordance with the procedure
described for the synthesis of keto acids 33 and 34, keto
acid 8 (0.896 g, 2.97 mmol, 1.0 equiv) in THF (10 mL) was
treated with lithium diisopropylamide [LDA; freshly
prepared from n-BuLi (4.36 mL, 1.6 M solution in hexanes,
7.41 mmol, 2.5 equiv) and diisopropylamine (960 mL, 6.83
mmol, 2.3 equiv) in THF (30 mL)] and aldehyde 7 (0.68 g,
5.3 mmol, 1.8 equiv) in THF (30 mL) to afford a mixture of
aldol products 45 and 46 in high yield and in a ca 3:2
ratio (1H NMR), along with unreacted keto acid 8 (5%). Rf
= 0.20 (silica gel, 50% EtOAc in hexanes); 1H NMR (500
MHz, CDCl3; only signals for 45 and 46 are reported) d
5.88-5.73 (m, 1 H, CH2CH=CH2), 5.04-4.92 (m, 2 H,
CH2CH=CH2), 4.51-4.47 (m, 0.4 H, CHOTBS), 4.44-4.40 (m,

0.6 H, (CH3)2CCH(OTBS)), 3.42 (d, J = 8.0 Hz, 0.4 H,
CHOH(CHCH3)), 3.32 (d, J= 9.0 Hz, 0.6 H, CHOH(CHCH3)),
3.30-3.20 (m, 1 H, CH3CH(C=O), 2.51-2.45 (m, 1 H,
CH2COOH), 2.38 (dd, J = 16.5, 6.5 Hz, 0.4 H, CH2COOH),
2.35 (dd, J = 16.5, 6.5 Hz, 0.6 H, CH2COOH), 2.11-1.98 (m,
2 H), 1.80-1.21 (m, 5 H), 1.20 (s, 1.8 H, C(CH3)2), 1.19
(s, 1.2 H, C(CH3)2), 1.16 (s, 1.8 H, C(CH3)2), 1.14 (s,
1.2 H, C(CH3)2), 1.06 (d, J = 6.5 Hz, 1.2 H), 1.05 (d, J =
6.5 Hz, 1.8 H), 1.00 (d, J = 6.5 Hz, 1.2 H), 0.89 (s, 5.4
H, SiC(CH3)3(CH3)2), 0.87 (s, 3.6 H, SiC(CH3)3(CH3)2),
0.85 (d, J =7.0 Hz, 1.8 H), 0.11 (s, 1.8 H,
SiC(CH3)3(CH3)2), 0.09 (s, 1.2 H, , SiC(CH3)3(CH3)2), 0.08
(s, 1.2 H, , SiC(CH3)3(CH3)2), 0.07 (s, 1.8 H,
SiC(CH3)3(CH3)2); HRMS (FAB), calcd for C23H44NaO5Si (M +
Na+) 451.2856, found 451.2867.

Synthesis of Hydroxy Esters 4 and 47 as illustrated
in Figure 7. EDC Coupling of Carboxylic Acids 45 and 46
and Alcohol 6. The crude mixture of keto acids 45 and 46
(1.30 g), 4-(dimethylamino)pyridine (4-DMAP, 0.037 g, 0.3
mmol), and alcohol 6 (1.90 g, 9.0 mmol;synthesized vida
infra as compound 91; eg. alcohol 6 as shown in figure 6
is the same compound as compound 91 as shown in figure 12)
in Methylene chloride (5 mL) was treated with 1-ethyl-(3-
dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC,
0.7 g, 3.6 mmol), according to the procedure described for
the synthesis of keto ester 22a, producing pure hydroxy
esters 4 (0.940 g, 52% from keto acid 8) and 47 (0.569 g,
31% from keto acid 8) after flash column chromatography

(silica gel, 18% EtOAc in hexanes). 4: Rf = 0.30 (silica
gel, 18% EtOAc in hexanes); [a]22D -53.4 (c 1.00, MeOH);
IR (film) nmax 3508, 2932, 1737, 1690, 1650, 1178, 1088,
835 cm-1; 1H-NMR (500 MHz, CDCl3): d 6.93 (s, 1 H, ArH),
6.47 (s, 1 H, ArCH=CCH3), 5.81-5.73 (m, 1 H, CH2CH=CH2),
5.73-5.65 (m, 1 H, CH2CH=CH2), 5.27 (dd, J = 7.0, 6.5 Hz,
1 H, CO2CH), 5.09 (d, J = 17.5 Hz, 1 H, CH2CH=CH2), 5.03
(d, J = 10.0 Hz, 1 H, CH2CH=CH2), 4.96 (d, J = 17.0 Hz, 1
H, CH2CH=CH2), 4.89 (d, J = 10.5 Hz, 1 H, CH2CH=CH2), 4.39
(dd, J = 6.0, 4.0 Hz, 1 H, (CH3)2CCH(OTBS)), 3.42 (bs, 1
H, CHOH(CHCH3)), 3.28 (q, J = 7.0 Hz; 1 H, CH3CH(C=O)),
3.24 (d, J = 9.5 Hz, 1 H, CHOH(CHCH3)), 2.67 (s, 3 H,
CH3Ar), 2.54-2.43 (m, 2 H), 2.43 (dd, J = 10.0, 4.0 Hz, 1
H, CH2COO), 2.31 (dd, J = 10.0, 6.0 Hz, 1 H, CH2COO), 2.04
(s, 3 H, ArCH=CCH3), 2.03-1.90 (m, 2 H, CH2CH=CH2), 1.75-
1.65 (m, 1 H), 1.48-1.43 (m, 1 H), 1.43-1.36 (m, 1 H),
1.22-1.10 (m, 2 H), 1.17 (s, 3 H, C(CH3)2), 1.09 (s, 3 H,
C(CH3)2), 1.01 (d, J = 6.5 Hz, 3 H, CH3CH(C=O)), 0.86 (s,
9 H, SiC(CH3)3(CH3)2), 0.81 (d, J = 7.0 Hz, 3 H CH3CHCH2),
0.09 (s, 3 H, SiC(CH3)3(CH3)2), 0.04 (s, 3 H,
SiC(CH3)3(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 221.8,
170.9, 164.6, 152.4, 139.0, 136.6, 133.2, 121.0, 117.8,
116.4, 114.1, 78.8, 74.5, 73.4, 53.9, 41.2, 40.1, 37.4,
35.4, 34.1, 32.3, 26.0, 25.9, 21.9, 19.9, 19.2, 18.1,
15.2, 14.6, 9.7, -4.3, -4.9; HRMS (FAB), calcd for
C34H57CsNO5SSi (M + Cs+) 752.2781, found 752.2760. 47:
Rf = 0.20 (silica gel, 18% EtOAc in hexanes); [a]22D -27.3
(c 1.00, CHCl3); IR (film) nmax 3509, 2932, 2857, 1737,
1691, 1465, 1381, 1292, 1253, 1177, 1088, 984, 835 cm-1;

1H NMR (500 MHz, CDC13) d 6.95 (s, 1 H, ArH), 6.49 (s, 1
H, ArCH=CCH3), 5.83-5.69 (m, 2 H, 2 x CH2CH=CH2), 5.29
(dd, J = 6.5, 6.5 Hz, 1 H, CO2CH), 5.11 (d, J = 17.0 Hz, 1
H, CH2CH=CH2), 5.05 (d, J = 10.0 Hz, 1 H, CH2CH=CH2), 5.01
(d, J = 17.0 Hz, 1 H, CH2CH=CH2), 4.95 01 (d, J = 10.5 Hz,
1 H, CH2CH=CH2), 4.50 (dd, J = 6.5, 4.0 Hz, 1 H,
(CH3)2CCH(OTBS)), 3.42 (dd, J = 8.0, 1.5 Hz, 1 H,
CHOH(CHCH3)), 3.21 (qd, J = 7.0, 2.0 Hz, 1 H, CH3CH(C=O)),
2.70 (s, 3 H, CH3Ar), 2.54-2.33 (m, 4 H), 2.11-1.98 (m, 2
H), 2.07 (s, 3 H, ArCH=CCH3), 1.53-0.98 (m, 5 H), 1.15 (s,
3 H, C(CH3)2), 1.11 (s, 3 H, C(CH3)2), 1.01 (d, J = 7 Hz,
3 H, CH3CH(C=O)), 0.99 (d, J = 6.5 Hz, 3 H, CH3CHCH2),
0.86 (s, 9 H, SiC(CH3)3(CH3)2), 0.08 (s, 3 H,
SiC(CH3)3(CH3)2), 0.07 08 (s, 3 H, SiC(CH3)3(CH3)2); 13C
NMR (125.7 MHz, CDC13) d 220.8, 170.9, 164.4, 152.2,
138.6, 136.6, 133.1, 120.9, 117.8, 116.3, 114.5, 78.8,
74.8, 72.5, 53.9, 41.3, 40.1, 37.4, 35.2, 33.7, 32.0,
25.9, 25.8, 21.7, 19.6, 19.1, 18.1, 15.4, 14.5, 10.5,
-4.4, -4.8; HRMS (FAB), calcd for C34H58NO5SSi (M + H+)
620.3805, found 620.3813.

**Synthesis of Hydroxy Lactones 3 and 48 as
illustrated in Figure 8.** Cyclization of Diene 42 via
Olefin Metathesis. A solution of diene 4 (0.186 g, 0.3
mmol) in Methylene chloride (200 mL, 0.0015 M) was treated
with bis(tricyclohexyl-phosphine)-benzylidine ruthenium
dichloride (RuCl2(=CHPh)(PCy3)2, 25 mg, 0.03 mol, 0.1
equiv; Aldrich), for 20 h, in accordance with the
procedure described for the synthesis of hydroxy lactone

25, producing hydroxy lactones 3 (83 mg, 46%) and 48 (70 mg, 39%) after flash chromatography (7 to 25% EtOAc in hexanes). 3: Rf = 0.18 (silica, 20% EtOAc in hexanes); [a]22D -79.5 (c = 1.00, CHCl3); IR (film) nmax 3422, 2930, 1739, 1688, 1255, 1180, 1090, 598 cm-1; 1H NMR (500 MHz, CDCl3) d 6.96 (s, 1 H, ArH), 6.55 (s, 1 H, ArCH=CCH3), 5.45 (ddd, J = 10.5, 10.5, 3.0 Hz, 1 H, CH=CHCH2), 5.35 (ddd, J = 10.5, 10.5, 5.5 Hz, 1 H, CH=CHCH2), 5.03 (d, J = 10.0 Hz, 1 H, CO2CH), 4.06 (t, J =6.0 Hz, 1 H, (CH3)2CCH(OTBS)), 3.94 (bs, 1 H, CHOH(CHCH3)), 3.05 (qd, J =6.5, 3.5 Hz, 1 H, CH3CH(C=O)), 3.00 (bs, 1 H, CHOH(CHCH3)), 2.80 (d, J = 6.0 Hz, 2 H, CH2COO), 2.78-2.69 (m, 1 H), 2.70 (s, 3 H, CH3Ar), 2.40-2.30 (m, 1 H), 2.10 (s, 3 H, ArCH=CCH3), 2.12-2.03 (m, 1 H), 2.00-1.93 (m, 1 H), 1.80-1.74 (m, 1 H), 1.70-1.58 (m, 1 H), 1.50-1.43 (m, 1 H), 1.30-1.15 (m, 2 H), 1.17 (s, 6 H, C(CH3)2), 1.14 (d, 3 H, J = 5.0 Hz, CH3CH(C=O)), 1.02 (d, 3 H, J =5.0 Hz, CH3CHCH2), 0.82 (s, 9 H, SiC(CH3)3(CH3)2), 0.12 (s, 3 H, SiC(CH3)3(CH3)2), -0.05 (s, 3 H, SiC(CH3)3(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 217.7, 170.7, 164.4, 152.2, 138.1, 134.5, 124.0, 119.5, 116.0, 79.0, 76.3, 73.2, 53.6, 43.1, 39.1, 38.9, 33.7, 32.0, 28.5, 28.0, 26.3, 24.9, 23.0, 19.3, 18.7, 16.6, 15.4, 14.3, -3.4, -5.3; HRMS (FAB), calcd for C32H53CsNO5SSi (M + Cs+) 724.2468, found 724.2466. 48: Rf = 0.40 (silica, 20% EtOAc in hexanes); [a]22D -71.5 (c = 0.80, CHCl3); IR (film) nmax 3381, 2958, 2928, 1727, 1273, 1122, 1072 cm-1; 1H NMR (600 MHz, CDCl3) d 7.00 (s, 1 H, ArH), 6.62 (s, 1 H, ArCH=CCH3), 5.36 (ddd, J = 15.0, 7.3, 7.3 Hz, 1 H, CH=CHCH2), 5.27 (ddd, J

= 15.0, 7.3, 7.3 Hz, 1 H, CH=CHCH2), 5.19 (dd, J =6.5, 3.6 Hz, 1 H, CO2CH), 4.43 (dd, J = 8.6, 2.7 Hz, 1 H, (CH3)2CCH(OTBS)), 3.87-3.83 (m, 1 H, CHOH(CHCH3)), 3.33-3.25 (bs, 1 H, CHOH(CHCH3)), 3.19 (qd, J = 6.9, 5.4 Hz, 1 H, CH3CH(C=O)), 2.71 (s, 3 H, CH3Ar), 2.72-2.67 (m, 1 H), 2.65 (dd, J = 15.4, 8.6 Hz, 1 H, CH2COO), 2.59 (dd, J = 15.4, 2.7 Hz, 1 H, CH2COO), 2.45-2.37 (m, 1 H), 2.20-2.12 (m, 1 H), 2.08 (s, 3 H, CH3C=CH), 2.00-1.93 (m, 1 H), 1.65-1.44 (m, 4 H), 1.22 (d, 3 H, J = 6.9 Hz, CH3CH(C=O)), 1.2-1.12 (m, 1 H), 1.15 (s, 3 H, C(CH3)2), 1.09 (s, 3 H, C(CH3)2), 1.03 (d, 3 H, J = 6.9 Hz, CH3CHCH2), 0.86 (s, 9 H, SiC(CH3)3(CH3)2), 0.08 (s, 3 H, SiC(CH3)3(CH3)2), 0.00 (s, 3 H, SiC(CH3)3(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 217.9, 169.9, 164.7, 152.1, 136.3, 134.5, 124.9, 119.4, 115.4, 77.4, 75.1, 74.1, 54.1, 43.9, 41.0, 38.5, 35.3, 33.0, 30.9, 27.0, 26.2, 23.8, 21.7, 19.1, 18.5, 17.0, 16.1, 14.8, -3.8, -4.2; HRMS (FAB), calcd for C32H53CsNO5SSi (M + Cs+) 724.2468, found 724.2479.

Synthesis of cis-Dihydroxy Lactone 49 as illustrated in Figure 8. Desilylation of Compound 3. Silyl ether 3 (30 mg, 0.05 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-Methylene chloride (0.3 mL, 0.17 M) at 0 oC. The reaction mixture was stirred at 0 °C for 3 h (completion of the reaction by TLC), and the solvents were evaporated under reduced pressure. The crude reaction mixture was purified by preparative thin layer chromatography (0.5 mm silica gel plate, 50% EtOAc in hexanes) to obtain-cis-

dihydroxy lactone 49 (22 mg, 90%). RF = 0.30 (silica gel, 50% EtOAc in hexanes); [a]22D -80.2 (c 1.36, CHCl3); IR (thin film) nmax 3453, 2929, 1733, 1686, 1506, 1464, 1250, 978 cm-1; 1H NMR (400 MHz, CDCl3) d 6.95 (s, 1 H, ArH), 6.59 (s, 1 H, ArCH=C(CH3)), 5.44 (ddd, J = 10.5, 10.5, 4.5 Hz, 1 H, CH=CHCH2), 5.36 (ddd, J = 10.5, 10.5, 5.0 Hz, 1 H, CH=CHCH2), 5.28 (d, J = 9.4 Hz, 1 H, CO2CH), 4.23 (d, J = 11.1 Hz, 1 H, (CH3)2CCH(OH)), 3.72 (m, 1 H, CHOH(CHCH3)), 3.43-3.37 (m, 1 H, OH), 3.14 (q, J = 6.7 Hz, 1 H, CH3CH(C=O)), 3.05 (bs, 1 H, OH), 2.72-2.63 (m, 1 H), 2.69 (s, 3 H, CH3Ar), 2.48 (dd, J = 14.8, 11.3 Hz, 1 H, CH2COO), 2.33 (dd, J = 14.8, 2.0 Hz, 1H, CH2COO), 2.30-2.13 (m, 2 H) 2.07 (s, 3 H, ArCH=CCH3), 2.07-1.98 (m, 1 H), 1.80-1.60 (m, 2H), 1.32 (s, 3 H, C(CH3)2), 1.36-1.13 (m, 3H), 1.17 (d, J = 6.8 Hz, 3 H, CH3CH(C=O)), 1.06 (s, 3 H, C(CH3)2), 0.99 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3) d 220.6, 170.4, 165.0 151.9, 138.7, 133.4, 125.0, 119.4, 115.8, 78.4, 74.1, 72.3, 53.3, 41.7, 39.2, 38.5, 32.4, 31.7, 27.6, 27.4, 22.7, 19.0, 18.6, 15.9, 15.5, 13.5; HRMS (FAB), calcd for C26H39CsNO5S (M + Cs+) 610.1603, found 610.1580.

Synthesis of trans-Dihydroxy Lactone 50 as illustrated in Figure 8. Desilylation of Compound 48. Silyl ether 48 (32 mg, 0.05 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)-Methylene chloride (0.3 mL, 0.17 M), according to the procedure described for cis-dihydroxy lactone 49, to yield, after preparative thin layer chromatography (0.5

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mm silica gel plate, 50% EtOAc in hexanes), trans-dihydroxy ester 50 (24 mg, 92%). Rf = 0.15 (silica gel, 50% EtOAc in hexanes); [a]22D -62.7 (c 1.65, CHCl3); IR (film) nmax 3428, 2932, 1730, 1692, 1468, 1253, 976 cm-1; 1H NMR (500 MHz, CDCl3) d 6.97 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=CCH3), 5.49 (ddd, J = 15.0, 4.7, 4.7 Hz, 1 H, CH=CHCH2), 5.38 (dd, J = 5.7, 5.7 Hz, 1 H, CO2CH), 5.37 (ddd, J = 15.0, 6.5, 6.5 Hz, 1 H, CH=CHCH2), 4.18 (d, J = 10.5 Hz, 1 H, (CH3)2CCH(OH)), 3.73 (m, 1 H, CHOH(CHCH3)), 3.27-3.20 (m, 2 H, CH3CH(C=O) and OH), 2.82 (bs, 1 H, OH), 2.70 (s, 3 H, CH3Ar), 2.55 (dd, J = 15.5, 10.5 Hz, 1 H, CH2COO), 2.48-2.43 (m, 3 H), 2.18-2.12 (m, 1 H), 2.07 (s, 3 H, ArCH=CCH3), 1.98-1.91 (m, 1 H), 1.63-1.55 (m, 2 H), 1.46 (dddd, J = 12.5, 12.5, 4.0, 4.0 Hz, 1 H), 1.27 (s, 3 H, C(CH3)2), 1.19 (m, 2 H), 1.17 (d, J = 6.5 Hz, 3 H, CH3CH(C=O)), 1.06 (s, 3 H, C(CH3)2), 0.97 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 219.8, 170.4, 164.9, 151.9, 137.1, 134.2, 125.6, 119.6, 115.9, 77.5, 75.7, 72.2, 52.5, 43.5, 38.8, 37.6, 36.1, 32.3, 31.2, 26.9, 21.3, 21.1, 19.1, 17.0, 15.7, 14.3; HRMS (FAB), calcd for C26H40NO5S (M + H+) 478.2627, found 478.2612.

Synthesis of Epothilones A (1) and 51-57 as illustrated in Figure 8. Epoxidation of cis-Dihydroxy Lactone 49. Procedure A: A solution of cis-dihydroxy lactone 49 (24 mg, 0.05 mmol) in CHCl3 (4.0 mL) was reacted with meta-chloroperbenzoic acid (mCPBA, 57-86%, 13.0 mg, 0.04-0.06 mmol, 0.8-1.2 equiv), at -20 to 0 °C,

according to the procedure described for the epoxidation
of 37, resulting in the isolation of epothilone A (1) (8.6
mg, 35%), its isomeric a-epoxide 51 (2.8 mg, 13%), and
compounds 52 (or 53) (1.6 mg, 9%), 53 (or 52) (1.5 mg,
7%), 54 (or 55) (1.0 mg, 5%), and 55 (or 54) (1.0 mg, 5%)
(stereochemistry unassigned for 52 and 53 and for 54 and
55), after two consecutive preparative thin layer
chromatographic purifications (250 mm silica gel plate, 5%
MeOH in Methylene chloride and 70% EtOAc in hexanes).
Procedure B: To a solution of cis-dihydroxy lactone 49
(15 mg, 0.03 mmol) in Methylene chloride (1.0 mL) at 0 °C
was added dropwise a solution of dimethyldioxirane in
acetone (ca 0.1 M, 0.3 mL, ca 1.0 equiv) until no starting
lactone was detectable by TLC. The solution was then
concentrated in vacuo and the crude product was subjected
to two consecutive preparative thin layer chromatographic
purifications (250 mm silica gel plate, 5% MeOH in
Methylene chloride and 70% EtOAc in hexanes), to obtain
pure epothilone A (1) (7.4 mg, 50%), its isomeric α-
epoxide 51 (2.3 mg, 15%), and epothilones 52 (or 53) (0.8
mg, 5%) and 53 (or 52) (0.8 mg, 5%) (stereochemistry
unassigned for 52 and 53. Procedure C: As described in
procedure B for the epoxidation of trans-hydroxy lactone
37, cis-dihydroxy lactone 49 (10.0 mg, 0.02 mmol) in MeCN
(200 mL) was treated with a 0.0004 M aqueous solution of
disodium salt of ethylenediaminetetraacetic acid (Na_2EDTA,
120 mL), excess 1,1,1-trifluoroacetone (100 mL), Oxone®
(61 mg, 0.10 mmol, 5.0 equiv) and NaHCO3 (14 mg, 0.16
mmol, 8.0 equiv), to yield, after purification by

preparative thin layer chromatography (250 mm silica gel plate, ether), a mixture of diastereomeric epoxides, epothilones A (1) (6.4 mg, 62%) and a-isomeric epoxide 51 (1.3 mg, 13%). Procedure D: A solution of cis-dihydroxy lactone 49 (18 mg, 0.037 mmol) in CHCl3 (1.0 mL) was treated with meta-chloroperbenzoic acid (mCPBA, 57-86 %, 15 mg, 0.049-0.074 mmol, 1.3-2.0 equiv), according to the procedure described for the epoxidation of 37, furnishing compounds 1 (2.7 mg, 15%), 51 (1.8 mg, 10%), 52 (or 53) (1.8 mg, 10%), 53 (or 52) (1.4 mg, 8%), 54 (or 55) (1.4 mg, 8%), 55 (or 54) (1.26 mg, 7%), 56 (0.9 mg, 5%), and 57 (0.9 mg, 5%) (stereochemistry unassigned for 52-57), after two consecutive preparative thin layer chromatographic purifications (250 mm silica gel plate, 5% MeOH in Methylene chloride and 70% EtOAc in hexanes). Epothilone A (1): Rf = 0.23 (silica gel, 33% MeOH-Methylene chloride); HPLC (Watman EOC, C-18, 4 m, 108 x 4.6 mm column, solvent gradient: 0 & 20 min, 30 & 80% MeOH in H2O) Rt = 14.8 min; [a]D = -45.0 (c 0.02, MeOH); IR (film) nmax 3476, 2974, 1738, 1692 cm-1; 1H-NMR (600 MHz, C6D6) d = 6.71 (s, 1 H, ArH), 6.45 (s, 1 H, ArCH=CCH3), 5.45 (dd, 1 H, J = 8.2, 2.3 Hz, CO2CH), 4.15 (dd, 1 H, J = 10.8, 2.9 Hz, (CH3)2CCH(OH)), 3.81-3.78 (m, 1 H, CHOH(CHCH3)), 3.65 (bs, 1 H, OH), 3.03 (qd, J = 6.9, 6.5 Hz, 1 H, CH3CH(C=O)), 2.77 (ddd, J = 7.9, 4.0, 4.0 Hz, 1 H, CH2CH-O(epoxide)CH), 2.62-2.58 (m, 1 H, CH2CH-O(epoxide)CH), 2.40 (dd, J = 14.4, 10.8 Hz, 1 H, CH2COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, CH3Ar), 2.19 (dd, J = 14.4, 2.9 Hz, 1 H, CH2COO), 2.05 (s, 3 H, ArCH=CCH3), 1.86 (ddd, J = 15.2,

2.5, 2.5 Hz, 1 H, CH2CH-O(epoxide)CH), 1.81-1.74 (m, 1 H,
CH2CH-O(epoxide)CH), 1.68 (ddd, J = 15.2, 7.6, 7.6 Hz, 1
H, CH2CH-O(epoxide)CH), 1.53-1.49 (m, 1 H, CH2CH-
O(epoxide)CH), 1.40-1.15 (m, 5 H), 1.06 (d, 3 H, J = 7.0
Hz, CH3CH(C=O)), 1.03 (s, 3 H, C(CH3)2), 0.97 (s, 3 H,
C(CH3)2), 0.95 (d, J = 6.9 Hz, 3 H, CH3CHCH2); 13C NMR
(150.9 MHz, C6D6) d 219.0, 170.2, 164.7, 153.0, 137.5,
119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8,
39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6, 18.7,
17.4, 15.7, 14.6; HRMS (FAB), calcd for C26H39CsNO6S (M +
Cs+) 626.1552, found 626.1531. 51: Rf = 0.35 (silica
gel, 70% EtOAc in hexanes); [a]22D -23.0 (c 0.10, CHCl3);
IR (film) nmax 3416, 2925, 2855, 1732, 1688, 1457 1258,
1150 cm-1; 1H NMR (500 MHz, C6D6) d 6.79 (s, 1 H, ArH),
6.57 (s, 1 H, ArCH=CCH3), 5.82 (d, J = 8.0 Hz, 1 H,
CO2CH), 4.31 (dd, J = 10.5, 2.5 Hz, 1 H, (CH3)2CCH(OH)),
4.19-4.15 (m, 1 H, CHOH(CHCH3)), 3.78 (bs, 1 H), 3.31 (qd,
J = 7.0, 3.0 Hz, 1 H, CH3CH(C=O)), 2.82 (ddd, J = 10.0,
4.2, 4.2 Hz, 1 H, CH2CH-O(epoxide)CH), 2.76 (bs, 1 H),
2.55 (ddd, J = 9.0, 9.0, 4.5 Hz, 1 H, CH2CH-O(epoxide)CH),
2.40 (dd, J = 13.0, 10.5, 1 H, CH2COO), 2.33 (dd, J =
13.0, 2.5 Hz, 1 H, CH2COO), 2.31 (s, 3 H, CH3Ar), 2.20 (s,
3 H, ArCH=CCH3), 1.97-1.92 (m, 1 H), 1.72 (ddd, J = 15.0,
8.5, 8.5 Hz, 1 H), 1.56 (ddd, J = 15.0, 4.5, 2.0 Hz, 1 H),
1.54-1.28 (m, 6 H), 1.17 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)),
1.13 (s, 3 H, C(CH3)2), 1.06 (d, J = 7.0 Hz, 3 H,
CH3CHCH2), 0.97 (s, 3 H, C(CH3)2); 13C NMR (150.9 MHz,
C6D6) d 221.7, 171.0, 165.5, 154.2, 138.3, 120.7, 117.6,
77.0, 74.8, 73.2, 57.7, 56.8, 52.4, 43.5, 39.5, 38.5,

33.0, 31.4, 28.3, 24.6, 21.6, 19.5, 19.2, 17.0, 15.7, 13.9; HRMS (FAB), calcd for $C_{26}H_{40}NO_6S$ (M + H+) 494.2576, found 494.2558. **52 (or 53):** Rf = 0.3 (silica gel, 30% EtOAc in hexanes); [a]22D -21.2 (c 0.17, CHCl3); IR (film) nmax 3477, 2926, 1740, 1686, 1465, 1259, 1060 cm-1; 1H NMR (500 MHz, C6D6) d 6.58 (s, 1 H, ArH), 5.44 (ddd, J = 10.5, 10.5, 5.0 Hz, 1 H, CH=CHCH2), 5.35 (ddd, J = 10.5, 10.5, 5.5 Hz, 1 H, CH=CHCH2), 5.23 (dd, J = 11.0, 2.0 Hz, 1 H, CO2CH), 5.05-4.98 (m, 1 H), 4.44 (s, 1 H, ArCH-O(epoxide)CCH3), 4.35 (dd, J = 11.5, 2.0 Hz, 1 H, (CH3)2CCH(OH)), 3.66-3.62 (m, 1 H, CHOH(CHCH3)), 3.46 (s, 1 H, OH), 2.93 (q, J = 7.0 Hz, 1 H, CH3CH(C=O)), 2.69 (ddd, J = 14.5, 11.0, 11.0 Hz, 1 H), 2.58 (dd, J = 14.0, 11.5 Hz, 1 H, CH2COO), 2.17 (s, 3 H, CH3Ar), 2.17-2.07 (m, 2 H), 2.06 (dd, J = 14.0, 2.0 Hz, 1 H, CH2COO), 1.90-1.78 (m, 2 H), 1.55-1.28 (m, 4 H), 1.23 (s, 3 H, C(CH3)2), 1.20 (s, 3 H, C(CH3)2), 1.15 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.05 (s, 3 H, ArCH-O(epoxide)CCH3), 1.01 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, C6D6) d 220.5, 169.7, 167.2, 151.0, 133.9, 124.2, 115.4, 74.5, 73.7, 71.9, 63.7, 59.2, 54.3, 40.9, 40.7, 38.2, 32.0, 29.1, 28.1, 26.9, 24.0, 18.3, 16.0, 15.6, 13.0 (two peaks overlapping); HRMS (FAB), calcd for $C_{26}H_{40}NO_6S$ (M + H+) 494.2576, found 494.2561. **53 (or 52):** Rf = 0.25 (silica gel, 30% EtOAc in hexanes); [a]22D +3.2 (c 0.25, CHCl3); IR (film) nmax 3333, 2928, 2855, 1737, 1686, 1463, 1381, 1248 cm-1; 1H NMR (500 MHz, C6D6) d 6.62 (s, 1 H, ArH), 5.67 (d, J = 6.5 Hz, 1 H, (CH3)2CCH(OH), 5.47 (dd, J = 11.5, 2.5 Hz, 1 H, CO2CH), 5.45-5.37 (m, 1 H, CH=CHCH2), 5.37-5.28 (m, 1

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H, CH=CHCH2), 4.44 (ddd, J = 12.0, 6.5, 2.5 Hz, 1 H,
(CH3)2CCH(OH)), 4.22 (s, 1 H, ArCH-O(epoxide)CCH3), 3.64
(d, J = 4.5 Hz, 1 H, CHOH(CHCH3)), 3.47 (s, 1 H,
CHOH(CHCH3)), 2.96 (q, J = 7.0 Hz, 1 H, CH3CH(C=O)), 2.60
(dd, J = 14.5, 12.0 Hz, 1 H, CH2COO), 2.55 (ddd, J = 15.5,
11.0, 11.0 Hz, 1 H), 2.20-2.02 (m, 2 H), 2.11 (s, 3 H,
CH3Ar), 1.99 (dd, J = 14.5, 2.5 Hz, 1 H, CH2COO), 1.90-
1.78 (m, 2 H), 1.58-1.49 (m, 1 H), 1.31 (s, 3 H, C(CH3)2),
1.28-0.85 (m, 3H), 1.25 (s, 3 H, ArCH-O(epoxide)CCH3),
1.25 (s, 3 H, C(CH3)2), 1.21 (d, J = 7.0 Hz, 3 H,
CH3CH(C=O)), 1.03 (d, J = 7.5 Hz, 3 H, CH3CHCH2); 13C NMR
(125.7 MHz, C6D6) d 219.8, 169.2, 167.1, 151.0, 133.2,
124.7, 114.8, 74.8, 73.6, 70.8, 64.7, 57.5, 54.1, 40.2,
39.6, 38.2, 31.8, 27.5, 27.2, 26.8, 24.1, 16.3, 15.9,
15.2, 15.0, 7.1; HRMS (FAB), calcd for C26H40NO6S (M + H+)
494.2576, found 494.2594. 54 (or 55): Rf = 0.20 (silica
gel, 70% EtOAc in hexanes); [a]22D -12.1 (c 0.14, CHCl3);
IR (film) nmax 3410, 2925, 2854, 1735, 1686, 1642, 1464
cm-1; 1H NMR (600 MHz, C6D6) d 6.52 (s, 1 H, ArH), 5.72
(d, J = 6.1 Hz, 1 H, OH), 5.42 (dd, J = 11.8, 2.0 Hz, 1 H,
CO2CH), 4.32-4.28 (m, 1 H, (CH3)2CCH(OH)), 4.05 (s, 1 H,
ArCH(-O)(epoxide)CCH3), 3.64 (bs, 1 H, CHOH(CHCH3)), 2.92-
2.86 (m, 1 H), 2.78-2.75 (m, 1 H), 2.66-2.63 (m, 1 H),
2.58 (dd, J = 14.0, 11.8 Hz, 1 H, CH2COO), 2.11 (d, J =
15.4 Hz, 1 H), 2.03 (s, 3 H, CH3Ar), 1.99 (dd, J = 14.0,
2.8 Hz, 1 H, CH2COO), 1.74-1.62 (m, 2 H), 1.61-1.52 (m, 2
H), 1.50-1.05 (m, 5 H), 1.20 (s, 3 H, C(CH3)2), 1.19 (s, 3
H, C(CH3)2), 1.18 (s, 3 H, ArCH-O(epoxide)CCH3), 1.10 (d,
J = 7.2 Hz, 3 H, CH3CH(C=O)), 0.84 (d, J = 7.2 Hz, 3 H,

CH3CHCH2); 13C NMR (125.7 MHz, C6D6) d 218.9, 170.3, 129.2, 115.9, 103.8, 74.7, 71.5, 65.6, 58.7, 57.9, 55.4, 55.2, 44.1, 40.7, 37.7, 32.2, 31.7, 29.1, 28.3, 24.5, 23.5, 18.9, 17.9, 17.5, 17.1, 7.2; HRMS (FAB), calcd for C26H40NO7S (M + H+) 510.2526, found 510.2511. 55 (or 54): Rf = 0.15 (silica gel, 70% EtOAc in hexanes); [a]22D -10.0 (c 0.15, CHC13); IR (film) nmax 3459, 2926, 2861, 1738, 1689, 1456 cm-1; 1H NMR (500 MHz, C6D6) d 6.56 (d, J = 1.0 Hz, 1 H, ArH), 5.55 (d, J = 4.0 Hz, 1 H, OH), 5.22 (dd, J = 11.5, 2.0 Hz, 1 H, CO2CH), 4.35 (s, 1 H, ArCH-O(epoxide)CCH3), 4.34-4.27 (m, 1 H, (CH3)2CCH(OH)), 3.71-3.68 (m, 1 H, CHOH(CHCH3)), 3.04-2.98 (m, 1 H), 2.95 (qd, J = 7.0, 3.5 Hz, CH3CH(C=O)), 2.88-2.83 (m, 1 H), 2.68-2.64 (m, 1 H), 2.61 (dd, J = 14.0, 11.5 Hz, 1 H, CH2COO), 2.21-2.16 (m, 1 H), 2.14 (s, 3 H, CH3Ar), 2.09 (dd, J = 14.0, 2.0 Hz, 1 H, CH2COO), 1.81-1.65 (m, 3 H), 1.49-1.31 (m, 6 H), 1.25 (s, 3 H, C(CH3)2), 1.20 (s, 3 H, C(CH3)2), 1.12 (d, J = 6.5 Hz, 3 H, CH3CH(C=O)), 0.96 (s, 3 H, ArCH-O(epoxide)CCH3), 0.88 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, C6D6) d 219.7, 169.5, 150.9, 124.2, 115.0, 74.9, 73.6, 71.2, 63.2, 58.9, 56.7, 53.7, 40.0, 35.1, 31.2, 29.7, 30.7, 28.6, 28.0, 24.1, 22.7, 17.2, 16.3, 16.0, 12.3, 11.9; HRMS (FAB), calcd for C26H39CsNO7S (M + Cs+) 642.1502, found 642.1521. 56: Rf = 0.10 (silica gel, 5% MeOH in Methylene chloride); [a]22D -110.0 (c 0.20, CHC13); IR (film) nmax 3222, 2928, 2855, 1737, 1683, 1462 cm-1; 1H NMR (500 MHz, CDC13) d 7.16 (s, 1 H, ArH), 5.84 (s, 1 H, ArCH=CCH3), 5.43 (ddd, J = 10.0, 10.0, 5.0 Hz, 1 H, CH=CHCH2), 5.42-5.35 (m, 1 H, CH=CHCH2), 5.40

(d, J = 10.0 Hz, 1 H, CO2CH), 4.90 (d, 1 H, J = 12.0 Hz, (CH3)2CCH(OH)), 3.76 (bs, 1 H), 3.75 (d, J = 5.0 Hz, 1 H, CHOH(CHCH3)), 3.15 (q, J = 7.0 Hz, 1 H, CH3CH(C=O)), 2.70 (dd, J = 12.5, 12.5 Hz, 1 H, CH2COO), 2.50 (ddd, J = 15.0, 10.0, 10.0 Hz, 1 H, CH=CHCH2), 2.21-2.12 (m, 2 H), 2.07 (dd, J = 13.0, 2.5 Hz, 1 H, CH2COO), 1.97 (s, 3 H, CH3Ar), 1.97-1.90 (m, 3 H), 1.63 (s, 3 H, ArCH=CCH3), 1.62-1.54 (m, 2 H), 1.46 (s, 3 H, C(CH3)2), 1.34 (s, 3 H, C(CH3)2), 1.26-1.16 (m, 3 H), 1.20 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.06 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, C6D6) d 221.0, 169.5, 144.0, 143.2, 142.7, 133.2, 125.0, 111.0, 109.0, 75.8, 73.8, 71.5, 55.0, 40.1, 38.5, 32.6, 31.6, 29.5, 27.6, 26.9, 23.9, 17.2, 15.3, 14.9, 13.2, 12.8; HRMS (FAB), calcd for C26H39CsNO6S 626.1552 (M + Cs+) 626.1552, found 626.1584. 57: Rf = 0.05 (silica gel, 5% MeOH in Methylene chloride); [a]22D -58.0 (c 0.10, CHCl3); IR (film) nmax 3340, 2921, 2851, 1736, 1686, 1459, 1248 cm-1; 1H NMR (500 MHz, CDCl3) d 7.13 (s, 1 H, ArH), 6.84 (s, 1 H, ArCH=CCH3), 5.34 (d, J = 11.0 Hz, 1 H, CO2CH), 4.55 (dd, 1 H, J = 10.0, 1.0 Hz, (CH3)2CCH(OH)), 3.74 (dd, J = 5.5, 2.0 Hz, 1 H, CHOH(CHCH3)), 3.25 (qd, J = 6.5, 1.5 Hz, 1 H, CH3CH(C=O)), 3.10-2.94 (m, 1 H), 2.70-2.64 (m, 2 H), 2.50 (dd, J = 12.5, 12.5 Hz, 1 H), 2.25 (d, J = 14.0 Hz, 1 H, CH2COO), 2.15 (dd, J = 14.0, 2.5 Hz, 1 H), 2.10 (s, 3 H, CH3Ar), 1.93-1.15 (m, 7 H), 1.46 (s, 3 H, ArCH=CCH3), 1.25 (s, 3 H, C(CH3)2), 1.20 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.04 (s, 3 H, C(CH3)2), 1.01 (d, J = 7.0 Hz, 3 H, CH3CHCH2); HRMS (FAB), calcd for C26H39CsNO7S (M + Cs+) 642.1502, found 642.1522.

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Synthesis of Compounds 54, 55, and 57 as illustrated in Figure 8. Oxidation of Epothilone A (1) with mCPBA. A solution of epothilone A (1) (3.0 mg, 0.006 mmol) in $CHC13$ (120 mL, 0.05 M) was reacted with meta-chloroperbenzoic acid (mCPBA, 57-86%, 1.1 mg, 0.0023-0.0032 mmol, 0.8-1.1 equiv; Aldrich), at -20 to 0 °C, according to the procedure described for the epoxidation of 37, resulting in the formation of bis(epoxides) 54 (or 55) (1.1 mg, 35%) and 55 (or 54) (1.0 mg, 32%) along with sulfoxide 57 (0.2 mg, 6%).

Synthesis of Epothilones 58-60 as illustrated in Figure 9. Epoxidation of trans-Dihydroxy Lactone 50. Procedure A: A solution of trans-dihydroxy lactone 50 (20 mg, 0.042 mmol) in $CHC13$ (4.0 mL) was treated with meta-chloroperbenzoic acid (mCPBA, 57-86%, 11.0 mg, 0.036-0.054 mmol, 0.9-1.3 equiv) at -20 to 0 °C, according to the procedure described for the epoxidation of compound 37, to give a epothilones 58 (or 59) (1.0 mg, 5%), 59 (or 58) (1.0 mg, 5%), and 60 (12 mg, 60%) (stereochemistry unassigned for all three), after preparative thin layer chromatography (250 mm silica gel plate, 70% EtOAc in hexanes). Procedure B: According to procedure B for the epoxidation of cis-dihydroxy lactone 49, a solution of trans-dihydroxy lactone 50 (10.0 mg, 0.02 mmol) in Methylene chloride (1.0 mL) was reacted with a solution of dimethyldioxirane (ca 0.1 M, 0.2 mL, ca 1.0 equiv) in acetone at 0 °C, and after preparative thin layer

chromatography (250 mm silica gel plate, 70% EtOAc in hexanes), epothilones 58 (or 59) (1.0 mg, 10%), 59 (or 58) (1.0 mg, 10%), and 60 (4.0 mg, 40%) were obtained.

Procedure C. As described in procedure B for the epoxidation of trans-hydroxy lactone 37, trans-dihydroxy lactone 50 (5.1 mg, 0.01 mol) in MeCN (100 mL) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na2EDTA, 60 mL), excess 1,1,1-trifluoroacetone (100 mL), Oxone® (32 mg, 0.05 mmol, 5.0 equiv) and NaHCO3 (7.0 mg, 0.08 mmol, 8.0 equiv), to yield, after purification by preparative thin layer chromatography (250 mm silica gel plate, ether), epothilones 58 (or 59) (2.3 mg, 45%) and 59 (or 58) (1.8 mg, 35%). 58 (or 59): Rf = 0.15 (silica gel, ether); [a]22D -23.3 (c 0.40, CHCl3); IR (film) nmax 3454, 2926, 2856, 1731, 1690, 1464, 1376, 1259, 1151, 980 cm-1; 1H NMR (500 MHz, C6D6) d 6.73 (s, 1 H, ArH), 6.53 (s, 1 H, ArCH=C(CH3)), 5.54 (dd, J = 8.0, 2.0 Hz, 1 H, CO2CH), 4.18 (d, J = 10.0 Hz, 1 H, (CH3)2CCH(OH)), 3.87 (dd, J = 4.5, 2.0 Hz, 1 H, CHOH(CHCH3)), 3.43 (bs, 1 H), 3.13 (dq, J = 7.0, 7.0 Hz, 1 H, CH3CH(C=O)), 2.74-2.72 (m, 1 H), 2.63-2.60 (m, 1 H), 2.45 (dd, J = 15.0, 10.5 Hz, 1 H, CH2COO), 2.33 (dd, J = 15.0, 3.0 Hz, 1 H, CH2COO), 2.32-2.24 (m, 1 H), 2.28 (s, 3 H, CH3Ar), 2.12 (s, 3 H, ArCH=CCH3), 2.00 (ddd, J = 15.0, 3.0, 2.5 Hz, 1 H), 1.75-1.65 (m, 3 H), 1.60-0.98 (m, 4 H), 1.18 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.10 (s, 3 H, C(CH3)2), 1.05 (s, 3 H, C(CH3)2), 0.97 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, C6D6) d 217.2, 170.3, 164.6, 153.2, 137.0, 120.4, 116.9, 76.7,

75.6, 72.8, 58.0, 56.0, 53.0, 44.7, 38.8, 36.5, 35.8,
32.0, 30.3, 30.1, 22.6, 21.0, 20.9, 17.1, 15.3, 14.9; HRMS
(FAB), calcd for C26H39CsNO6S (M + Cs+) 626.1552, found
626.1538. 59 (or 58): Rf = 0.2 (silica gel, ether);
[a]22D -25.3 (c 0.30, CHCl3); IR (film) nmax 3419, 2923,
1732, 1691, 1464, 1259 cm-1; 1H NMR (500 MHz, C6D6) d
6.82 (s, 1 H, ArH), 6.56 (s, 1 H, ArCH=C(CH3)), 5.53 (dd,
J = 7.5, 3.5 Hz, 1 H, CO2CH), 4.47 (d, J = 8.5 Hz, 1 H,
(CH3)2CCH(OH)), 3.94 (bs, 1 H, CHOH(CHCH3)), 3.65-3.58 (m,
1 H), 3.35 (dq, J = 6.5, 6.5 Hz, 1 H, CH3CH(C=O)), 2.73-
2.65 (m, 1 H), 2.65-2.61 (m, 1 H), 2.52-2.46 (m, 1 H),
2.41 (dd, J = 14.0, 9.5 Hz, 1 H, CH2COO), 2.33 (dd, J =
14.0, 4.0 Hz, 1 H, CH2COO), 2.31 (s, 3 H, CH3Ar), 2.03 (s,
3 H, ArCH=CCH3), 1.91-1.81 (m, 2 H), 1.78-1.53 (m, 4 H),
1.41-1.32 (m, 2 H), 1.22 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)),
1.21 (s, 3 H, C(CH3)2), 1.08 (d, J = 7.0 Hz, 3 H,
CH3CHCH2), 1.05 (s, 3 H, C(CH3)2); 13C NMR (150.9 MHz,
C6D6) d 215.7, 167.6, 161.7, 149.8, 133.8, 116.6, 113.4,
73.8, 73.2, 70.1, 55.2, 52.4, 49.9, 41.7, 36.4, 34.0,
32.3, 28.0, 27.8, 27.4, 19.9, 17.8, 15.8, 14.6, 13.0,
12.3; HRMS (FAB), calcd for C26H39CsNO6S (M + Cs+)
626.1552, found 626.1531. 60: Rf = 0.6 (silica gel, 70%
EtOAc in hexanes); [a]22D -28.3 (c 0.30, CHCl3); IR (film)
nmax 3472, 2928, 1735, 1691, 1466 cm-1; 1H NMR (500 MHz,
C6D6) d 6.67 (s, 1 H, ArH), 5.48-5.41 (m, 1 H, CH=CHCH2),
5.36-5.23 (m, 2 H, CH=CHCH2 and CO2CH), 4.36-4.30 (m, 1 H,
(CH3)2CCH(OH)), 3.79-3.73 (m, 1 H), 3.63-3.58 (m, 1 H),
3.17-3.10 (m, 1 H, CH3CH(C=O)), 2.81 (bs, 1 H), 2.53 (dd,
J = 15.0, 10.5 Hz, 1 H, CH2COO), 2.40-2.29 (m, 2 H), 2.26-

2.19 (m, 2 H), 2.25 (s, 3 H, CH3Ar), 2.20-1.95 (m, 1 H),
1.80-1.72 (m, 1 H), 1.62-1.53 (m, 1 H), 1.46-1.33 (m, 2
H), 1.20 (d, J = 6.5 Hz, 3 H, CH3CH(C=O)), 1.13 (s, 3 H,
C(CH3)2), 1.10 (s, 3 H, C(CH3)2), 1.08 (d, J = 7.0 Hz, 3
H, CH3CHCH2), 1.06 (s, 3 H, ArCH-O(epoxide)CCH3); 13C NMR
(125.7 MHz, C6D6) d 219.7, 169.6, 166.9, 151.3, 135.4,
124.6, 115.8, 78.3, 72.8, 72.6, 64.2, 59.1, 53.3, 43.4,
40.2, 38.8, 34.3, 33.1, 31.4, 27.5, 21.8, 19.8, 18.9,
16.5, 15.3, 14.0; HRMS (FAB), calcd for C26H40NO6S (M +
H+) 494.2576, found 494.2587.

**Synthesis of Dihydroxy Ester 61 as illustrated in
Figure 10.** Desilylation of Compound 47. Silyl ether 47
(48 mg, 0.079 mmol) was treated with a freshly prepared
solution of 20% (v/v) trifluoroacetic acid (TFA)-Methylene
chloride (1.6 mL, 0.05 M), according to the procedure
described for the desilylation of compound 3, to yield,
after flash column chromatography (silica gel, 5% & 50%
EtOAc in hexanes), dihydroxy ester 61 (35 mg, 90%). Rf =
0.68 (silica gel, 50% EtOAc in hexanes); [a]22D -18.0 (c
0.40, CHCl3); IR (film) nmax 3420, 2931, 1732, 1383, 1177,
979 cm-1; 1H NMR (500 MHz, CDCl3) d 6.97 (s, 1 H, ArH),
6.54 (s, 1 H, ArCH=CCH3), 5.82-5.70 (m, 2 H, 2 x
CH2CH=CH2), 5.37 (dd, J = 7.0, 7.0 Hz, 1 H, CO2CH), 5.10
(d, J = 17.0 Hz, 1 H, CH2CH=CH2), 5.07 (d, J = 10.0 Hz, 1
H, CH2CH=CH2), 5.00 (d, J = 17.0 Hz, 1 H, CH2CH=CH2), 4.95
(d, J = 10.0 Hz, 1 H, CH2CH=CH2), 4.24 (dd, J = 10.0, 2.0
Hz, 1 H, (CH3)2CCHOH), 3.50 (dd, J = 8.0, 3.0 Hz, 1 H,
CHOH(CHCH3)), 3.26 (qd, J = 6.5, 2.5 Hz, 1 H, CH3CH(C=O)),

2.70 (s, 3 H, CH3Ar), 2.52-2.46 (m, 2 H), 2.41 (dd, J = 16.5, 10.5 Hz, 1 H, CH2COO), 2.08 (s, 3 H, ArCH=CCH3), 2.08-1.99 (m, 2 H, CH2CH=CH2), 1.60-1.06 (m, 6 H), 1.17 (s, 6 H, C(CH3)2), 1.07 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.97 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 221.5, 171.9, 164.7, 152.1, 138.7, 136.7, 133.1, 120.9, 117.9, 116.4, 114.5, 78.7, 74.8, 72.3, 52.1, 41.4, 37.5, 36.8, 35.0, 33.8, 32.3, 25.7, 21.5, 19.1, 19.0, 15.2, 14.7, 11.5; HRMS (FAB), calcd for C28H43CsNO5S (M + Cs+) 638.1916, found 638.1902.

Synthesis of Dihydroxy Lactones 62 and 63 as illustrated in Figure 10. Olefin Metathesis of Dihydroxy Ester 61. A solution of compound 61 (48 mg, 0.095 mmol) in Methylene chloride (20 mL, 0.005 M) was treated with bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (RuCl2(=CHPh)(PCy3)2, 16 mg, 0.019 mmol, 0.2 equiv; Figure 10), according to the procedure described for the cyclization of 25, producing dihydroxy lactones 62 (9.1 mg, 20%) and 63 (32 mg, 69%), after preparative thin layer chromatograpy (0.5 mm silica gel plate, 33% EtOAc in hexanes). 62: Rf = 0.30 (silica gel, 6% MeOH in Methylene chloride); [a]22D -93.1 (c 0.10, CHCl3); IR (thin film) nmax 3450, 2929, 1735, 1685, 1464, 1380, 1250, 1182, 1045, 978, 732 cm-1; 1H NMR (600 MHz, CDCl3) d 6.96 (s, 1 H, ArH), 6.51 (s, 1 H, ArCH=CCH3), 5.58 (dd, J = 9.5, 2.0 Hz, 1 H, CO2CH), 5.56 (ddd, J = 9.8, 9.8, 6.5 Hz, 1 H, CH=CHCH2), 5.37 (ddd, J = 9.8, 9.8, 4.5 Hz, 1 H, CH=CHCH2), 4.25 (d, J = 10.0 Hz, 1 H,

(CH3)2CCH(OH)), 3.55 (d, J = 9.6 Hz, 1 H, CHOH(CHCH3)),
3.39 (bs, 1 H, OH), 3.31 (q, J = 6.9 Hz, 1 H, CH3CH(C=O)),
2.99 (bs, 1 H, OH), 2.71 (s, 3 H, CH3Ar), 2.69-2.61 (m, 1
H, CH=CHCH2), 2.59 (dd, J = 16.3, 1.5 Hz, 1 H, CH2COO),
2.41 (dd, J = 16.3, 10.0 Hz, 1 H, CH2COO), 2.45-2.35 (m, 1
H, CH=CHCH2), 2.20-2.10 (m, 1 H, CH=CHCH2), 2.08 (s, 3 H,
ArCH=CCH3), 1.98-1.90 (m, 1 H, CH=CHCH2), 1.59-1.50 (m, 1
H), 1.49-1.30 (m, 4 H), 1.17 (s, 3 H, C(CH3)2), 1.11 (d, J
= 6.9 Hz, 3 H, CH3CH(C=O)), 1.03 (s, 3 H, C(CH3)2), 1.01
(d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3)
d 222.2, 171.1, 165.2, 153.5, 139.5, 133.2, 125.1, 120.0,
116.7, 78.4, 74.1, 72.9, 52.5, 40.7, 39.5, 37.9, 34.5,
32.7, 31.3, 27.6, 24.7, 22.2, 18.9, 17.5, 15.5, 15.3; HRMS
(FAB), calcd for C26H39NO5S (M + H+) 478.2627, found
478.2610. 63: Rf = 0.69 (silica gel, 50% EtOAc in
hexanes); [a]22D -68.3 (c 1.30, CHC13); IR (film) nmax
3498, 2932, 1730, 1694, 1383, 1260, 1154, 1076, 1043, 974,
756 cm-1; 1H NMR (500 MHz, CDCl3) d 6.95 (s, 1 H, ArH),
6.49 (s, 1 H, ArCH=CCH3), 5.50 (t, J = 6.5 Hz, 1 H,
CO2CH), 5.48 (ddd, J = 15.0, 7.0, 6.0 Hz, 1 H, CH=CHCH2),
5.36 (ddd, J = 15.0, 6.5, 6.5 Hz, 1 H, CH=CHCH2), 4.24
(dd, J = 10.5, 1.0 Hz, 1 H, (CH3)2CCHOH), 3.55 (d, J = 9.5
Hz, 1 H, CHOH(CHCH3)), 3.37 (q, J = 7.0 Hz, 1 H,
CH3CH(C=O)), 2.69 (s, 3 H, CH3Ar), 2.58 (dd, J = 15.5, 1.5
Hz, 1 H, CH2COO), 2.50-2.48 (m, 2 H, CH=CHCH2), 2.39 (dd,
J = 15.5, 10.5 Hz, 1 H, CH2COO), 2.16-2.08 (m, 1 H,
CH=CHCH2), 2.08 (s, 3 H, ArCH=CCH3), 1.97-1.91 (m, 1 H,
CH=CHCH2), 1.62-1.56 (m, 1 H), 1.41-1.11 (m, 4 H), 1.20
(s, 3 H, C(CH3)2), 1.12 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)),

1.03 (s, 3 H, C(CH3)2), 0.98 (d, J = 6.5 Hz, 3 H,
CH3CHCH2); 13C NMR (125.7 MHz, CDC13) d 221.8, 171.1,
164.8, 152.1, 136.7, 134.2, 124.9, 119.8, 116.4, 78.1,
74.6, 73.2, 52.8, 40.9, 38.3, 36.1, 34.6, 32.9, 32.9,
24.9, 22.9, 19.2, 17.7, 16.0, 15.5, 11.5; HRMS (FAB),
calcd for C26H39CsNO5S (M + Cs+) 610.1603, found 610.1587.

**Synthesis of Epothilones 64-65 as illustrated in
Figure 10.** Epoxidation of cis-Dihydroxy Lactone 62.
Procedure A: A solution of cis-dihydroxy lactone 62 (10.0
mg, 0.021 mmol) in CHC13 (210 mL) was treated with meta-
chloroperbenzoic acid (mCPBA, 57-86%, 5.0 mg, 0.0165-
0.0252 mmol, 0.8-1.2 equiv) at -20 & 0 °C, according to
the procedure described for the epoxidation of compound
37, to produce, after preparative thin layer
chromatography (250 mm silica gel plate, 70% EtOAc in
hexanes), epothilones 64 (or 65) (2.6 mg, 25%) and 65 (or
64) (2.4 mg, 23%) (stereochemistry unassigned for all
three). Procedure B. As described in procedure B for the
epoxidation of trans-hydroxy lactone 37, cis-dihydroxy
lactone 62 (10.0 mg, 0.021 mmol) in MeCN (400 mL) was
treated with a 0.0004 M aqueous solution of disodium salt
of ethylenediaminetetraacetic acid (Na2EDTA, 200 mL),
excess 1,1,1-trifluoroacetone (150 mL), Oxone® (65 mg,
0.105 mmol, 5.0 equiv) and NaHCO3 (14 mg, 0.168 mmol, 8.0
equiv), to yield, after purification by preparative thin
layer chromatography (250 mm silica gel plate, ether),
epothilones 64 (or 65) (6.0 mg, 58%) and 65 (or 64) (3.0
mg, 29%). 64 (or 65): Rf = 0.23 (silica gel, 6% MeOH in

Methylene chloride); [a]22D -20.0 (c 0.20, CHCl3); IR
(thin film) nmax 3448, 2919, 1725, 1684, 1455, 1378, 1284,
1149, 1061, 1020, 973, 750 cm-1; 1H NMR (500 MHz, CDCl3) d
6.99 (s, 1 H, ArH), 6.68 (s, 1 H, ArCH=CCH3), 5.64-5.61
(m, 1 H, CO2CH), 4.43 (d, J = 2.1 Hz, 1 H, (CH3)2CCH(OH),
4.29 (ddd, J = 7.6, 2.5, 2.5 Hz, 1 H, (CH3)2CCH(OH)), 3.82
(d, J = 8.2 Hz, 1 H, CHOH(CHCH3)), 3.35 (bs, 1 H,
CHOH(CHCH3), 3.22 (q, J = 7.0 Hz, 1 H, CH3CH(C=O)), 3.14
(ddd, J = 10.3, 4.1, 3.2 Hz, 1 H, CH2CH-O(epoxide)CH),
2.90 (ddd, J = 10.3, 4.3, 2.3 Hz, 1 H, CH2CH-
O(epoxide)CH), 2.71 (s, 3 H, CH3Ar), 2.54 (dd, J = 13.7,
7.6 Hz, 1 H, CH2COO), 2.51 (dd, J = 13.7, 2.5 Hz, 1 H,
CH2COO), 2.21-2.19 (m, 1 H), 2.18 (s, 3 H, ArCH=CCH3),
1.94 (ddd, J = 15.3, 10.3, 3.7 Hz, 1 H), 1.77-1.69 (m, 2
H), 1.60-1.00 (m, 5 H), 1.15 (s, 3 H, C(CH3)2), 1.14 (d, J
= 6.9 Hz, 3 H, CH3CH(C=O)), 1.06 (s, 3 H, C(CH3)2), 1.02
(d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz,
CHCl3) d 221.8, 172.1, 165.1, 152.6, 134.7, 119.8, 116.8,
76.0, 74.4, 72.8, 56.4, 53.8, 53.0, 40.2, 39.1, 34.1,
32.7, 29.4, 27.8, 22.7, 20.9, 19.0, 16.1, 15.9, 15.0,
11.8; HRMS (FAB), calcd for C26H40NO6S (M + H+) 494.2576,
found 494.2587. 65 (or 64): Rf = 0.22 (silica gel, 6%
MeOH in Methylene chloride); [a]22D -42.5 (c 0.20, CHCl3);
IR (thin film) nmax 3384, 2890, 1738, 1685, 1451, 1375,
1155, 1061, 1064 cm-1; 1H NMR (600 MHz, CDCl3) d 6.99 (s,
1 H, ArH), 6.58 (s, 1 H, ArCH=CCH3), 5.88 (d, J = 10.4 Hz,
1 H, CO2CH), 4.74 (d, J = 9.8 Hz, 1 H, (CH3)2CCH(OH)),
3.70-3.65 (m, 2 H, CHOH(CHCH3) and OH), 3.45-3.40 (m, 2 H,
CH3CH(C=O) and OH), 3.19 (ddd, J = 9.7, 3.8, 2.1 Hz, 1 H,

CH2CH-O(epoxide)CH), 3.08 (ddd, J = 9.0, 4.5, 4.5 Hz, 1 H,
CH2CH-O(epoxide)CH), 2.71 (s, 3 H, CH3Ar), 2.51 (d, J =
13.8, 1 H, CH2COO), 2.45 (dd, J = 13.7, 9.8 Hz, 1 H,
CH2COO), 2.18-2.02 (m, 2 H), 2.11 (s, 3 H, ArCH=CCH3),
1.80-0.96 (m, 7 H), 1.16 (s, 3 H, C(CH3)2), 1.13 (d, J =
7.0 Hz, 3 H, CH3CH(C=O)), 1.05 (s, 3 H, C(CH3)2), 1.03 (d,
J = 6.8 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CHCl3) d
222.2, 171.1, 164.8, 151.8, 136.6, 120.3, 116.7, 76.9,
73.7, 72.9, 56.6, 54.8, 52.8, 40.2, 38.8, 34.1, 33.0,
31.7, 25.0, 23.3, 20.4, 19.4, 16.7, 15.8, 15.6, 11.9; HRMS
(FAB), calcd for C26H39CsNO6S (M + Cs+) 626.1552, found
626.1573.

**Synthesis of Epothilones 67-69 as illustrated in
Figure 10.** Epoxidation of trans-Dihydroxy Lactone. 63.
Procedure A. A solution of trans-dihydroxy lactone 63
(17.0 mg, 0.033 mmol) in CHCl3 (2.0 mL) was treated with
meta-chloroperbenzoic acid (mCPBA, 57-86%, 8.9 mg, 0.029-
0.044 mmol, 0.9-1.3 equiv) at -20 to 0 °C, according to
the procedure described for the synthesis of epoxide 37,
to produce, after preparative thin layer chromatography
(250 mm silica gel plate, 70% EtOAc in hexanes),
epothilones 67 (or 68) (4.2 mg, 24%), 68 (or 67) (3.3 mg,
19%) and 69 (5.4 mg, 31%) (stereochemistry unassigned for
all three). Procedure B. As described in procedure C for
the epoxidation of cis-lactone 49, trans-dihydroxy lactone
63 (6.0 mg, 0.0126 mmol) in MeCN (240 mL) was treated with
a 0.0004 M aqueous solution of disodium salt of
ethylenediaminetetraacetic acid (Na2EDTA, 90 mL), 1,1,1-

trifluoroacetone (90 mL), Oxone® (40 mg, 0.063 mmol, 5.0
equiv) and NaHCO3 (8.4 mg, 0.100 mmol, 8.0 equiv), to
yield, after purification by preparative thin layer
chromatography (250 mm silica gel plate, ether),

5 epothilones 67 (or 68) (2.7 mg, 44%) and 68 (or 67) (1.3
mg, 21%). 67 (or 68): Rf = 0.47 (silica gel, 50% EtOAc
in hexanes); [a]22D -27.3 (c 0.30, CHC13); IR (film) nmax
3459, 2932, 1732, 1152, 978 cm-1; 1H NMR (600 MHz, CDC13)
d 6.97 (s, 1H, ArH), 6.57 (s, 1 H, ArCH=CCH3), 5.72 (d, J

10 = 10.4 Hz, 1 H, CO2CH), 4.41 (d, J = 9.8 Hz, 1 H,
(CH3)2CCH(OH)), 4.27 (bs, 1 H, OH), 3.76 (d, J = 6.1 Hz, 1
H, CHOH(CHCH3)), 3.27 (q, J = 7.0 Hz, 1 H, CH3CH(C=O),
2.94-2.88 (m, 1 H), 2.75-2.71 (m, 1 H), 2.70 (s, 3 H,
CH3Ar), 2.49 (d, J = 12.9 Hz, 1 H, CH2COO), 2.41 (dd, J =

15 12.9, 9.8 Hz, 1 H, CH2COO), 2.18-2.11 (m, 1 H), 2.09 (s, 3
H, ArCH=CCH3), 1.95-1.87 (m, 1 H), 1.80-1.00 (m, 5 H),
1.16 (s, 3 H, C(CH3)2), 1.14 (d, 3 H, J = 6.9 Hz,
CH3CH(C=O)), 1.04 (s, 3 H, C(CH3)2), 0.92 (d, 3 H, J = 6.9
Hz, CH3CHCH2); 13C NMR (125.7 MHz, CDC13) d 220.4, 171.9,

20 164.7, 151.9, 136.5, 120.2, 116.6, 76.9, 74.5, 73.6, 58.1,
56.0, 53.1, 42.2, 39.2, 36.2, 34.7, 33.1, 29.4, 22.4,
21.9, 19.3, 16.2, 15.2, 13.7, 12.4; ; HRMS (FAB), calcd
for C26H40NO6S (M + H+) 494.2576, found 494.2561. 68 (or
67): Rf = 0.46 (silica gel, 50% EtOAc in hexanes); [a]22D

25 -55.2 (c 0.25, CHC13); IR (film) nmax 3442, 2931, 1731,
1687, 1153, 982, 732 cm-1; 1H NMR (600 MHz, CDC13) d 6.97
(s, 1 H, ArH), 6.57 (s, 1 H, ArCH=CCH3), 5.56 (dd, J =
8.6, 3.1 Hz, 1 H, CO2CH), 4.23 (d, J = 9.3 Hz, 1 H,
(CH3)2CCH(OH)), 3.73 (dd, J = 7.4, 1.1 Hz, 1 H,

CHOH(CHCH3)), 3.57 (bs, 1 H), 3.34 (dq, J = 7.0, 1.3 Hz, CH3CH(C=O)), 3.12 (bs, 1 H), 2.76 (dt, J = 5.5, 2.2 Hz, 2 H), 2.72-2.68 (m, 1 H), 2.71 (s, 3 H, CH3Ar), 2.61 (dd, J = 15.4, 1.6 Hz, 1 H, CH2COO), 2.41 (dd, J = 15.4, 10.6 Hz, 1 H, CH2COO), 2.15 (ddd, J = 15.0, 5.1, 3.5 Hz, 1 H), 2.07 (s, 3 H, ArCH=CCH3), 1.91-1.86 (m, 1 H), 1.76-1.17 (m, 5 H), 1.29 (s, 3 H, C(CH3)2), 1.30 (s, 3 H, C(CH3)2), 1.12 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 0.95 (d, J = 6.7 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3) d 221.2, 171.2, 164.9, 151.8, 135.9, 120.1, 116.6, 77.1, 74.0, 72.8, 58.7, 55.8, 52.7, 42.3, 38.4, 35.3, 35.1, 33.0, 32.0, 22.6, 22.0, 19.3, 18.5, 15.5, 15.2, 12.2; HRMS (FAB), calcd for C26H40NO6S (M + H+) 494.2562, found 494.2576. 69: . Rf = 0.67 (silica gel, 50% EtOAc in hexanes); [a]22D -30.5 (c = 0.40, CHCl3); IR (film) nmax 3500, 2932, 1732, 1693, 1184, 975 cm-1; 1H NMR (600 MHz, CDCl3) d 6.95 (s, 1 H, ArH), 5.51 (ddd, J = 14.3, 7.0, 7.0 Hz, 1 H, CH=CHCH2), 5.37 (ddd, J = 14.3, 7.1, 7.1 Hz, 1 H, CH=CHCH2), 5.16 (dd, J =9.2, 3.4 Hz, 1 H, CO2CH), 4.20 (d, J = 10.7 Hz, 1 H, (CH3)2CCH(OH)), 4.16 (s, 1 H, OH), 3.48 (d, J = 9.2 Hz, 1 H, CHOH(CHCH3)), 3.37 (q, J = 6.9 Hz, 1 H, CH3CH(C=O), 2.70 (s, 3 H, CH3Ar), 2.62 (d, J = 15.7 Hz, 1 H, CH2COO), 2.60-2.54 (m, 1 H), 2.50-2.43 (m, 1 H), 2.38 (dd, J = 15.7, 10.7 Hz, 1 H, CH2COO), 2.23-2.15 (m, 1 H, CH=CHCH2), 2.00-1.92 (m, 1 H, CH=CHCH2), 1.80-1.00 (m, 5 H), 1.24 (s, 3 H, C(CH3)2), 1.20 (s, 3 H, C(CH3)2), 1.10 (d, 3 H, J = 6.9 Hz, CH3CH(C=O), 1.02 (s, 3 H, ArCH-O(epoxide)CCH3), 0.98 (d, 3 H, J = 6.7 Hz, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 221.4, 170.9, 166.3, 150.6, 135.4, 124.3, 115.4,

74.8, 74.1, 73.1, 63.0, 58.8, 52.7, 41.1, 38.1, 34.8, 33.5, 33.2, 32.9, 25.2, 22.9, 19.3, 18.1, 16.1, 13.4, 11.7; HRMS (FAB), calcd for $C_{26}H_{40}NO_6S$ (M + H+) 494.2576, found 494.2587.

Synthesis of Alcohol 85 as illustrated in Figure 12. Allylboration of Keto Aldehyde 84. Aldehyde 84 (16.0 g, 0.125 mol; Inuka, T.; Yoshizawa, R. J. Org. Chem. 1967, 32, 404-407) was dissolved in ether (400 mL) and cooled to -100 °C. To this solution was added (+)-diisopinocampheylallylborane (800 mL, 0.15 M in pentane, 0.125 mol, 1.0 equiv) by cannulation during 45 min. [(+)-Diisopinocampheylallylborane in pentane is prepared by the adaptation of the standard methods reported by Brown]. Allyllmagnesium bromide (66.0 mL, 1 M solution in ether, 0.066 mol) was added dropwise to a well stirred solution of (-)-B-methoxydiisopinocampheyl borane (20.9 g, 0.066 mol) in ether (400 mL) at 0 oC. After the completion of the addition, the reaction mixture was stirred at room temperature for 1 h and the solvent was removed under reduced pressure. The residue was extracted with pentane (3 x 400 mL) under argon and stirring was discontinued to allow precipitation of the magnesium salts. The clear pentane solution was cannulated into another flask using a double ended needle through a Kramer filter and used without further purification. After the addition was complete, the mixture was stirred at the same temperature for 30 min. Methanol (20 mL) was added at -100 °C, and the reaction mixture was allowed to reach room

temperature. To this solution was added saturated aqueous NaHCO3 solution (200 mL), followed by H2O2 (80 mL of 50% solution in H2O) and the reaction mixture was allowed to stir at room temperature for 12 h. The reaction mixture was extracted with EtOAc (3 x 200 mL), and the organic extracts were combined, washed with saturated aqueous NH4Cl solution (100 mL) and dried (Na2SO4). Evaporation of the solvents followed by flash column chromatography (silica gel, 3% acetone in Methylene chloride) resulted in pure alcohol 85 (14.6 g, 74%). 85: colorless oil; Rf = 0.20 (silica gel, 3% acetone in Methylene chloride); [a]22D -4.0 (c 1.5, CHCl3); IR (thin film) nmax 3492, 2976, 2939, 1699, 1641, 1469, 1379, 1087, 1020, 990, 973, 914 cm-1; 1H NMR (600 MHz, CDCl3) d 5.85-5.80 (m, 1 H, CH=CH2), 5.11-5.07 (m, 2 H, CH=CH2), 3.73 (dd, J = 10.5, 2.0 Hz, 1 H, CHOH), 2.54-2.40 (m, 3 H), 2.25-2.18 (m, 1 H), 2.03-1.96 (m, 1 H), 1.14 (s, 3 H, C(CH3)2), 1.10 (s, 3 H, C(CH3)2), 0.99 (t, J = 7.0 Hz, 3 H, CH3CH2); 13C NMR (150.9 MHz, CDCl3) d 217.2, 135.6, 117.7, 75.5, 51.2, 36.4, 31.3, 21.8, 19.5, 7.8; FAB HRMS (NBA/NaI) m/e 193.1200, M + Na+ calcd for C10H18O2 193.1204.

Synthesis of Ketone 86 as illustrated in Figure 12. Silylation of Alcohol 85. Alcohol 85 (11.0 g, 0.0647 mol) was dissolved in Methylene chloride (200 mL), the solution was cooled at -78 °C, and 2,6-lutidine (10.5 mL, 0.0906 mol, 1.4 equiv) was added. After stirring for 5 min at that temperature, tert-butyldimethylsilyl triflate (19.3 mL, 0.0841 mol, 1.3 equiv) was added dropwise and

the reaction mixture was allowed to stir at -78 oC for 45 min, after which time no starting material was detected by TLC. Saturated aqueous NH4Cl solution (30 mL) was added, and the reaction mixture was allowed to warm up to room temperature. The organic phase was separated, and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were dried (MgSO4), filtered through celite and the solvents were removed under reduced pressure. Purification by flash column chromatography (silica gel, 2 to 10% ether in hexanes) gave pure 86 (18.0 g, 98%): Rf = 0.75 (silica gel, 20% ether in hexanes); [a]22D +2.6 (c 0.8, CHCl3); IR (thin film) nmax 2935, 1705, 1467, 1362, 1254, 1089, 911, 836, 775 cm-1; 1H NMR (600 MHz, CDCl3) d 5.78-5.71 (m, 1 H, CH=CH2), 5.01-4.94 (m, 2 H, CH=CH2), 3.97 (dd, J = 6.2, 5.2 Hz, 1 H, CHOSi), 2.54 (dq, J = 14.3, 7.2 Hz, 1 H, CH2CH3), 2.44 (dq, J = 14.2, 7.1 Hz, 1 H, CH2CH3), 2.21-2.16 (m, 1 H, CH2CH=CH2), 2.14-2.08 (m, 1 H, CH2CH=CH2), 1.10 (s, 3 H, C(CH3)2), 1.07 (s, 3 H, C(CH3)2), 0.98 (t, J = 7.1 Hz, 3 H, CH3CH2), 0.87 (s, 9 H, SiC(CH3)3), 0.05 (s, 3 H, Si(CH3)2), 0.01 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 215.9, 136.2, 116.5, 76.7, 52.9, 39.0, 31.9, 26.0, 22.4, 20.1, 18.2, 7.7, -3.6, -4.4.

Synthesis of Keto Aldehyde 87 as illustrated in Figure 12. Ozonolysis of Ketone 86. Alkene 86 (2.84 g, 10 mmol) was dissolved in Methylene chloride (25 mL) and the solution was cooled to -78 °C. Oxygen was bubbled through for 2 min after which time ozone was passed through until the reaction mixture adopted a blue color

(ca 30 min). The solution was then purged with oxygen for 2 min at -78 °C (disappearance of blue color) and Ph3P (3.16 g, 12.0 mmol, 1.2 equiv) was added. The cooling bath was removed and the reaction mixture was allowed to reach room temperature and stirred for an additional 1 h. The solvent was removed, under reduced pressure and the mixture was purified by flash column chromatography (silica gel, 25% ether in hexanes) to provide pure keto aldehyde 87 (2.57 g, 90%): Rf = 0.45 (silica gel, 20% ether in hexanes); $[\alpha]22D$ -1.9 (c 4.0, CHCl3); IR (thin film) nmax 2935, 2858, 1707, 1467, 1388, 1255, 1093, 1004, 837, 777 cm-1; 1H NMR (500 MHz, CDCl3) d 9.78 (dd, J = 2.1, 2.0 Hz, CHO), 4.55 (dd, J = 6.0, 4.5 Hz, 1 H, CHOSi), 2.59-2.44 (m, 4 H, CH2CH3, CH2CH=O), 1.13 (s, 3 H, C(CH3)2), 1.09 (s, 3 H, C(CH3)2), 1.00 (t, J = 7.0 Hz, 3 H, CH3CH2), 0.85 (s, 9 H, (CH3)3C), 0.06 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 215.3, 200.9, 71.3, 52.3, 48.5, 31.9, 25.8, 21.3, 20.4, 18.0, 7.5, -4.4, -4.9; FAB HRMS (NBA/NaI) m/e 309.1854, M + Na+ calcd for C15H30O3Si 309.1862.

Synthesis of Keto Acid 76 as illustrated in Figure 12. Oxidation of Keto Aldehyde 87. Aldehyde 87 (2.86 g, 10 mmol), tBuOH (50 mL), isobutylene (20 mL, 2 M solution in THF, 40 mmol, 4.0 equiv), H2O (10 mL), NaClO2 (2.71 g, 30.0 mmol, 3.0 equiv) and NaH2PO4 (1.80 g, 15.0 mmol, 1.5 equiv) were combined and stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was subjecte. to flash column

chromatography (silica gel, 50% ether in hexanes) to produce pure keto acid 76 (2.81 g, 93%). Rf = 0.12 (silica gel, 20% ether in hexanes); $[\alpha]22D$ +16.1 (c 1.0, CHCl3); IR (thin film) nmax 2934, 2858, 1710, 1467, 1254, 1093, 834 cm-1; 1H NMR (600 MHz, CDCl3) d 4.46 (dd, J = 7.0, 3.6 Hz, 1 H, CHOSi), 2.64-2.34 (m, 3 H, CH2CH3, CH2COOH), 2.32 (q, J = 7.0 Hz, 1 H, CH2CH3), 1.13 (s, 3 H, C(CH3)2), 1.11 (s, 3 H, C(CH3)2), 0.99 (t, J = 7.0 Hz, 3 H, CH3CH2), 0.83 (s, 9 H, (CH3)3C), 0.04 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 215.1, 178.2, 73.4, 52.4, 39.2, 31.6, 25.8, 20.8, 20.5, 18.0, 7.6, -4.5, -5.0; FAB HRMS (NBA) m/e 303.1996, M+ H+ calcd for C15H30O3Si 303.1992.

Synthesis of Aldehyde 89 as illustrated in Figure 12. Reduction of Ester 88. Ethyl ester 88 (52.5 g, 0.306 mol; Aldrich) was dissolved in Methylene chloride (1 L) and cooled to -78 °C. DIBAL (490.0 mL, 1 M solution in Methylene chloride, 0.4896 mol, 1.6 equiv) was added dropwise via a cannula while the temperature of the reaction mixture was maintained at -78 oC. After the addition was complete, the reaction mixture was stirred at the same temperature until its completion was verified by TLC (ca 1 h). Methanol (100 mL) was added at -78 °C and was followed by addition of EtOAc (1 L) and saturated aqueous NH4Cl solution (300 mL). The quenched reaction mixture was allowed to warm up to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 200 mL).

The combined organic phase was dried over MgSO4, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 to 90% ether in hexanes) furnished the desired aldehyde 89 (33.6 g, 90%): Rf = 0.68 (silica gel, ether); IR (thin film) nmax 3095, 2828, 1695, 1485, 1437, 1378, 1334, 1178, 1129, 1011 cm-1; 1H NMR (500 MHz, CDCl3) d 9.96 (s, 1 H, CHO), 8.0 (s, 1 H, SCH=C), 2.77 (s, 3 H, N=C(S)CH3); 13C NMR (125.7 MHz, CDCl3) d 184.2, 167.5, 154.8, 128.0, 19.1; FAB HRMS (NBA/NaI) m/e 149.9992, M + Na+ calcd for C5H5NOS 149.9990.

Synthesis of Aldehyde 90 as illustrated in Figure 12. Aromatic aldehyde 89 (31.1 g, 0.245 mol) was dissolved in benzene (500 mL) and 2-(triphenylphosphoranilidene)-propionaldehyde (90.0 g, 0.282 mol, 1.15 equiv) was added. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca 2 h). Evaporation of the solvent under reduced pressure, followed by flash column chromatography (10 to 90% ether in hexanes) produced the desired aldehyde 90 (40.08 g, 98%): Rf = 0.78 (silica gel, ether); IR (thin film) nmax 3089, 1675, 1624, 1190, 1141, 1029, 947.6, 881 cm-1; 1H NMR (500 MHz, CDCl3) d 9.57 (s, 1 H, CHO), 7.46 (s, 1 H), 7.26 (s, 1 H), 2.77 (s, 3 H, N=C(S)CH3), 2.20 (s, 3 H, CH=C(CHO)CH3); 13C NMR (125.7 MHz, CDCl3) d 195.3, 165.7, 151.9, 140.9, 138.2, 122.6, 19.2, 10.9; FAB HRMS (NBA) m/e 168.0481, M + H+ calcd for C8H9NOS 168.0483.

Synthesis of Alcohol 91 as illustrated in Figure 12. Allylboration of Aldehyde 90. Aldehyde 90 (20.0 g, 0.120 mol) was dissolved in anhydrous ether (400 mL) and the solution was cooled to -100 °C. (+)-Diisopinocampheylallyl borane (1.5 equiv in pentane, prepared from 60.0 g of (-)-Ipc2BOMe and 1.0 equiv of allyl magnesium bromide according to the method described for the synthesis of alcohol 85), was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol (40 mL) was added at -100 oC, and the reaction mixture was allowed to warm up to room temperature. Amino ethanol (72.43 mL, 1.2 mol, 10.0 equiv) was added and stirring was continued for 15 h. The work-up procedure was completed by the addition of saturated aqueous NH4Cl solution (200 mL), extraction with EtOAc (4 x 100 mL) and drying of the combined organic layers with MgSO4. Filtration, followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol 91 (24.09 g, 96%): Rf = 0.37 (60% ether in hexanes); [a]22D -20.2 (c 1.0, CHCl3); IR (thin film) nmax 3357, 2923, 1642, 1505, 1437, 1322, 1186, 1018, 914, 878 cm-1; 1H NMR (600 MHz, CDCl3) d 6.81 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH3), 5.87-5.79 (m, 1 H, CH=CH2), 5.02 (d, J = 17.1 Hz, 1 H, CH=CH2), 4.97 (d, J = 10.3 Hz, 1 H, CH=CH2), 4.12 (dd, J = 7.8, 5.0 Hz, 1 H,

CHOH), 3.8 (bs, 1 H, OH), 2.59 (s, 3 H, N=C(S)CH3), 2.31
(dd, J = 7.0, 6.5 Hz, 2 H, CH2=CHCH2), 1.91 (s, 3 H,
CH=CCH3); 13C NMR (150.9 MHz, CDCl3) d   164.5, 152.5,
141.8, 134.8, 118.7, 117.1, 115.1, 76.3, 39.8, 18.8, 14.1;
FAB HRMS (NBA) m/e 210.0956, M + H+ calcd for C11H15NOS
210.0953.

**Synthesis of Compound 92 as illustrated in Figure
12. Silylation of Alcohol 91.** Alcohol 91 (7.0 g, 0.033
mol) was dissolved in DMF (35 mL, 1.0 M), the solution was
cooled to 0 °C and imidazole (3.5 g, 0.050 mol, 1.5 equiv)
was added. After stirring for 5 min, tert-
butyldimethylsilyl chloride (6.02 g, 0.040 mol, 1.2 equiv)
was added portionwise and the reaction mixture was allowed
to stir at 0 °C for 45 min, and then at 25 °C for 2.5 h,
after which time no starting alcohol was detected by TLC.
Methanol (2 mL) was added at 0 oC and the solvent was
removed under reduced pressure. Ether (100 mL) was added,
followed by saturated aqueous NH4Cl solution (20 mL), the
organic phase was separated and the aqueous phase was
extracted with ether (2 x 20 mL). The combined organic
solution was dried (MgSO4), filtered over celite and the
solvents were removed under reduced pressure. Flash
column chromatography (silica gel, 10 to 20% ether in
hexanes) provided pure 92 (10.8 g, 99%): Rf = 0.70 (40%
ether in hexanes); [α]22D +1.39 (c 3.0, CHCl3); IR (thin
film) nmax 2931, 2060, 1496, 1460, 1249, 1173, 1073, 908,
837, 779 cm-1; 1H NMR (600 MHz, CDCl3) d   6.91 (s, 1 H,
SCH=C), 6.45 (s, 1 H, CH=CCH3), 5.80-5.75 (m, 1 H,

CH=CH2), 5.03 (ddd, J = 17.1, 3.5, 1.5 Hz, 1 H, CH=CH2),
4.99 (ddd, J = 10.2, 2.1, 0.9 Hz, 1 H, CH=CH2), 4.14 (dd,
J = 6.6, 6.1 Hz, 1 H, CHOH), 2.69 (s, 3 H, N=C(S)CH3),
2.37-2.32 (m, 1 H, CH2=CHCH2), 2.31-2.25 (m, 1 H,
CH2=CHCH2), 1.99 (s, 3 H, CH=CCH3), 0.88 (s, 9 H,
SiC(CH3)3), 0.05 (s, 3 H, Si(CH3)2), 0.00 (s, 3 H,
Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d   165.2, 153.9,
142.9, 136.2, 119.7, 117.4, 115.9, 79.3, 42.1, 26.7, 20.1,
19.0, 14.8, -3.8, -4.1; FAB HRMS (NBA) m/e 324.1804, M +
H+ calcd for C17H29NOSSi 324.1817.

**Synthesis of Aldehyde 82 as illustrated in Figure
12.** Dihydroxylation of Olefin 92 and 1,2 Glycol Cleavage.
Olefin 92 (16.7 g, 51.6 mmol) was dissolved in THF/tBuOH
(1 : 1, 500 mL) and H2O (50 mL). 4-Methylmorpholine N-
oxide (NMO) (7.3 g, 61.9 mmol, 1.2 equiv) was added at 0
°C, followed by OsO4 (5.2 mL, solution in tBuOH 1.0 mol%,
2.5% by weight). The mixture was vigorously stirred for
2.5 h at 0 °C and then for 12 h at 25 °C. After
completion of the reaction, Na2SO3 (5.0 g) was added at 0
°C, followed by H2O (100 mL). Stirring was continued for
another 30 min and then ether (1 L) was added, followed by
saturated aqueous NaCl solution (2 x 100 mL). The organic
phase was separated and the aqueous phase was extracted
with ether (2 x 100 mL). The combined organic extracts
were dried (MgSO4), filtered, and the solvents were
removed under reduced pressure. Flash column
chromatography (silica gel, ether to EtOAc) provided 17.54
g (95%) of the expected 1,2-diol as a 1:1 mixture of

diastereoisomers: Rf = 0.55 (silica gel, EtOAc); IR (thin film) nmax 3380, 2931, 2856, 1656, 1505, 1465, 1460, 1254, 1187, 1073, 908, 837, 777 cm-1; 1H NMR (500 MHz, CDCl3) d 6.90 and 6.88 (singlets, 1 H total, SCH=C), 6.52 and 6.47 (singlets, 1 H total, CH=CCH3), 4.44-4.39 (m, 1 H), 3.95-3.84 (m, 1 H), 3.81-3.72 and 3.63-3.34 (m, 4 H total), 2.66 and 2.65 (singlets, 3 H total, N=C(S)CH3), 1.96 and 1.95 (singlets, 3 H total), 1.82-1.75 and 1.69-1.56 (m, 2 H total), 0.87 and 0.86 (singlets, 9 H total, SiC(CH3)3), 0.08 and -0.01 (singlets, 3 H total, Si(CH3)2), 0.07 and 0.10 (singlets, 3 H total, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 164.6, 164.5, 152.8, 152.4, 141.6, 141.5, 119.4, 118.4, 115.3, 115.2, 78.0, 75.4, 70.4, 68.8, 66.8, 66.5, 38.9, 38.7, 25.7, 19.0, 18.9, 18.0, 17.9, 14.6, 13.5, -4.6, -4.8, -5.2, -5.4; FAB HRMS (NBA/NaI) m/e 380.1699, M + Na+ calcd for C17H31NO3SSi 380.1692.

The diol obtained from 92 as described above (5.2 g, 14.5 mmol) was dissolved in EtOAc (150 mL) and cooled to 0 °C. Pb(OAc)4 (8.1 g, 95% purity, 18.3 mmol, 1.2 equiv) was then added portionwise over 10 min, and the mixture was vigorously stirred for 15 min at 0 °C. After completion of the reaction, the mixture was filtered through silica gel and washed with 60% ether in hexanes. The solvents were then removed under reduced pressure providing pure aldehyde 82 (4.7 g, 98%): Rf = 0.76 (silica gel, 60% ether in hexanes); [a]22D -20.3 (c 1.4, CHCl3); IR (thin film) nmax 2931, 2856, 1726, 1504, 1466, 1389, 1254, 1182, 1087, 999, 839, 784 cm-1; 1H NMR (500 MHz, CDCl3) d 9.69 (dd, J = 2.7, 2.2 Hz, 1 H, CHO), 6.86 (s, 1 H, SCH=C), 6.48 (s,

1 H, CH=CCH3), 4.60 (dd, J = 8.2, 3.9 Hz, 1 H, CHOSi),
2.64 (ddd, J = 15.5, 8.3, 2.9 Hz, 1 H, CHOCH2), 2.59 (s, 3
H, N=C(S)CH3), 2.41 (ddd, J = 15.5, 4.0, 2.0 Hz, 1 H,
CHOCH2), 1.95 (s, 3 H, CH=CCH3), 0.79 (s, 9 H, SiC(CH3)3),
0.00 (s, 3 H, Si(CH3)2), -0.06 (s, 3 H, Si(CH3)2); 13C NMR
(125.7 MHz, CDCl3) d 201.0, 164.5, 152.4, 140.3, 119.0,
115.8, 73.7, 49.9, 25.6, 18.9, 17.9, 13.9, -4.8, -5.4; FAB
HRMS (NBA) m/e 326.1615, M + H+ calcd for C16H27NO2SSi
326.1610.

**Synthesis of Alcohol 93 as illustrated in Figure
12. Reduction of Aldehyde 82.** A solution of aldehyde 82
(440 mg, 1.35 mmol) in MeOH (13 mL) was treated with NaBH4
(74 mg, 2.0 mmol, 1.5 equiv) at 0 °C for 15 min. The
solution was diluted with ether (100 mL) and then
saturated aqueous NH4Cl solution (5 mL) was carefully
added. The organic phase was washed with brine (10 mL),
dried (MgSO4) and concentrated. Flash column
chromatography (silica gel, 60% ether in hexanes) gave
alcohol 93 (425 mg, 96%) as a colorless oil. 26: Rf =
0.52 (silica gel, 60% ether in hexanes); [a]22D -29.4 (c
0.8, CHCl3); IR (thin film) nmax 3362, 2950, 2856, 1656,
1505, 1466, 1362, 1254, 1186, 1075, 839, 777 cm-1; 1H NMR
(500 MHz, CDCl3) d 6.86 (s, 1 H, SCH=C), 6.40 (s, 1 H,
CH=CCH3), 4.30 (dd, J = 7.6, 5.3 Hz, 1 H, CHOSi), 3.69-
3.59 (m, 2 H, CH2OH), 3.15 (s, 1 H, OH), 2.61 (s, 3 H,
N=C(S)CH3), 1.92 (s, 3 H, CH=CCH3), 1.82-1.76 (m, 1 H,
CH2CH2OH), 1.73-1.67 (m, 1 H, CH2CH2OH), 0.82 (s, 9 H,
SiC(CH3)3), 0.02 (s, 3 H, Si(CH3)2), -0.05 (s, 3 H,

Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 164.3, 152.7,
141.6, 118.5, 115.1, 76.6, 59.6, 38.3, 25.8, 18.9, 18.0,
14.0, -4.8, -5.4; FAB HRMS (NBA/CsI) m/e 460.0727, M + Cs+
calcd for C16H29NO2SSi 460.0743.

Synthesis of Iodide 94 as illustrated in Figure 12.
Iodination of Alcohol 93. A solution of alcohol 93 (14.0
g, 42.7 mmol) in ether: MeCN (3:1, 250 mL) was cooled to 0
°C. Imidazole (8.7 g, 128.1 mmol, 3.0 equiv), Ph3P (16.8
g, 64.1 mmol, 1.5 equiv), and iodine (16.3 g, 64.1 mmol,
1.5 equiv) were sequentially added and the mixture was
stirred for 0.5 h at 0 °C. A saturated aqueous solution
of Na2S2O3 (50 mL) was added, followed by the addition of
ether (600 mL). The organic phase was washed with brine
(50 mL), dried (MgSO4), and the solvents were removed
under vacuum. Flash column chromatography (silica gel,
15% ether in hexanes) gave pure iodide 94 (16.6 g, 89%) as
a colorless oil: Rf = 0.40 (silica gel, 10% ether in
hexanes); [a]22D +11.0 (c 1.0, CHCl3); IR (thin film) nmax
2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836,
777 cm-1; 1H NMR (600 MHz, CDCl3) d 6.90 (s, 1 H, SCH=C),
6.53 (s, 1 H, CH=CCH3), 4.19 (dd, J = 7.7, 4.5 Hz, 1 H,
CHOSi), 3.18 (t, J = 7.3 Hz, 2 H, CH2I), 2.67 (s, 3 H,
N=C(S)CH3), 2.10-2.05 (m, 1 H, CH2CH2I), 2.01-1.95 (m, 1
H, CH2CH2I), 1.99 (s, 3 H, CH=CCH3), 0.87 (s, 9 H,
SiC(CH3)3), 0.09 (s, 3 H, Si(CH3)2), 0.00 (s, 3 H,
Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 164.4, 152.7,
140.9, 119.3, 115.4, 78.0, 40.2, 25.8, 19.2, 18.1, 13.9,
3.1, -4.6, -5.0; FAB HRMS (NBA) m/e 438.0768, M + H+ calcd

for C16H28INOSSi 438.0784.

Synthesis of Phosphonium Salt 79 as illustrated in Figure 12.. A mixture of iodide 94 (16.5g, 37.7 mmol) and Ph3P (10.9 g, 41.5 mmol, 1.1 equiv) was heated neat at 100 ˚C for 2 h. Purification by flash column chromatography (silica gel, Methylene chloride; then 7% MeOH in Methylene chloride) provided phosphonium salt 79 (25.9 g, 98%) as a white solid: Rf = 0.50 (silica gel, 7% MeOH in Methylene chloride); [a]22D +3.7 (c 0.7, CHCl3); IR (thin film) nmax 2951, 2856, 1503, 1466, 1253, 1179, 1081, 936, 884, 836, 777 cm-1; 1H NMR (600 MHz, CDCl3) d 7.78-7.28 (m, 15 H, aromatic), 6.97 (s, 1 H, SCH=C), 6.57 (s, 1 H, CH=CCH3), 4.48 (dd, J = 6.3, 4.8 Hz, 1 H, CHOSi), 3.72-3.65 (m, 1 H, CH2P), 3.31-3.25 (m, 1 H, CH2P), 2.61 (s, 3 H, N=C(S)CH3), 1.91 (s, 3 H, CH=CCH3), 1.95-1.86 (m, 1 H, CH2CH2P), 1.82-1.74 (m, 1 H, CH2CH2 P), 0.83 (s, 9 H, SiC(CH3)3), 0.07 (s, 3 H, Si(CH3)2), -0.02 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 164.4, 152.3, 139.4, 135.1, 133.3, 133.2, 130.5, 130.4, 128.1, 119.8, 117.9, 117.3, 116.5, 76.0, 28.9, 25.7, 19.1, 18.4, 17.9, 14.5, -4.8.

Synthesis of Hydrazone 95 as illustrated in Figure 13. Alkylation of Hydrazone 80. Hydrazone 80 (20.0 g, 117.0 mmol, 1.0 equiv), dissolved in THF (80 mL), was added to a freshly prepared solution of LDA [19.75 mL of diisopropylamine (141.0 mmol, 1.2 equiv) was added to a solution of 88.1 mL of 1.6 M solution of n-BuLi in hexanes

(141 mmol, 1.2 equiv) in 160 mL of THF at 0 °C] at 0 °C.
After stirring at this temperature for 8 h, the resulting
yellow solution was cooled to -100 °C, and a solution of
4-iodo-1-benzyloxybutane (36.0 g, 124.0 mmol, 1.2 equiv)
in THF (40 mL) was added dropwise over a period of 30 min.
The mixture was allowed to warm to room temperature over 8
h, and was then poured into saturated aqueous NH4Cl
solution (40 mL) and extracted with ether (3 x 200 mL).
The combined organic extracts were dried (MgSO4), filtered
and evaporated. Purification by flash column
chromatography on silica gel (20% ether in hexanes)
provided hydrazone 95 as a yellow oil (35.8 g, 92%, de >
98% by 1H NMR): Rf = 0.45 (silica gel, 50% ether in,
hexanes); [a]22D -55.0 (c 1.2, CHCl3); IR (thin film) nmax
2929, 2862, 1603, 1455, 1362, 1198, 1108, 737, 698 cm-1;
1H NMR (500 MHz, CDCl3) d 7.33 (s, 5 H, Ph), 6.48 (d, J
= 6.5 Hz, 1 H, CH=NN), 4.46 (s, 2 H, CH2Ph), 3.54 (dd, J =
9.0, 3.8 Hz, 1 H, CH2OCH3), 3.44 (t, J = 6.5 Hz, 2 H,
CH2OBn), 3.40 (dd, J = 9.0, 6.8 Hz, 1 H, CH2OCH3), 3.33
(s, 3 H, OCH3), 2.65 (m, 1 H, CHCH2OCH3), 2.29 (m, 1 H,
CH(CH3)C=N), 1.94-1.76 (m, 4 H), 1.61 (m, 2 H), 1.45-1.36
(m, 6 H), 1.01 (d, J = 6.8 Hz, 3 H, CHCH3); 13C NMR (125.7
MHz, CDCl3) d 144.6, 138.6, 128.2, 127.5, 127.3, 74.7,
72.7, 70.2, 63.4, 59.1, 50.4, 37.0, 35.2, 29.7, 26.4,
23.7, 22.0, 18.9; FAB HRMS (NBA) m/e 333.2552, M + H+
calcd for C20H32N2O2 333.2542.

Synthesis of Aldehyde 96 as illustrated in Figure
13. Cleavage of Hydrazone 95. Procedure A: A solution

of hydrazone 95 (13.0 g, 39.1 mmol) in Methylene chloride
(50 mL) was treated with ozone at -78 °C until the
solution turned blue-green. The solution was purged with
oxygen for 2 min at -78 °C, allowed to warm to room

5   temperature, and then concentrated. The crude mixture so
obtained was purified by flash column chromatography
(silica gel, 10% ether in hexanes) to give aldehyde 96
(6.6 g, 77%) as a colorless oil. Procedure B: A solution
of hydrazone 95 (30 g, 90.3 mmol) in MeI (100 mL) was

10   heated at 60 °C. After 5 h, the reaction was complete
(TLC), and the mixture was concentrated. The resulting
crude product was suspended in n-pentane (360 mL) and was
treated with 3 N aqueous HCl (360 mL). The two-phase
system was vigorously stirred for 1 h, and the aqueous

15   phase was extracted with n-pentane (3 x 200 mL). The
combined organic solution was dried (MgSO4), concentrated
and purified by flash column chromatography (silica gel,
10% ether in hexanes) to give 96 (17.1 g, 86%): Rf = 0.49
(silica gel, 50% ether in hexanes); [a]22D +11.6 (c 1.7,

20   CHCl3); IR (thin film) nmax 2932, 2856, 1715, 1450, 1361,
1272, 1202, 1102, 920, 732, 697 cm-1; 1 H NMR (500 MHz,
CDCl3) d 9.60 (d, J = 2.0 Hz, 1 H, CHO), 7.34 (s, 5 H,
Ph), 4.50 (s, 2 H, CH2Ph), 3.47 (t, J = 6.5 Hz, 2 H,
CH2OBn), 2.33 (m, 1 H, CH(CH3)CO), 1.75-1.69 (m, 1 H),

25   1.65-1.61 (m, 2 H), 1.49-1.34 (m, 3 H), 1.08 (d, J = 7.0
Hz, 3 H, CHCH3); 13C NMR (125.7 MHz, CDCl3) d 205.0,
138.4, 128.2, 127.5, 127.4, 72.8, 69.9, 46.1, 30.1, 29.6,
23.6, 13.2; FAB HRMS (NBA) m/e 221.1538, M + H+ calcd for
C14H20O2 221.1542.

Synthesis of Alcohol 97 as illustrated in Figure 13. Reduction of Aldehyde 96. A solution of aldehyde 96 (17.0 g, 77.0 mmol) in MeOH (200 mL) was treated with NaBH4 (8.6 g, 228 mmol, 3.0 equiv) at 0 °C for 15 min. The solution was then diluted with ether (400 mL) and saturated aqueous NH4Cl solution (50 mL) was carefully added. The organic phase was washed with brine (50 mL), dried (MgSO4), and concentrated. The crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol 97 (16.8 g, 98%) as a colorless oil: Rf = 0.23 (silica gel, 50% ether in hexanes); [a]22D -5.1 (c 1.9, CHCl3); IR (thin film) nmax 3401, 2931, 2860, 1455, 1361, 1267, 1202, 1102, 1037, 937, 732, 697 cm-1; 1H NMR (500 MHz, CDCl3) d 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH2Ph), 3.50 (dd, J = 11.0, 6.0 Hz, 1 H, CH2OH), 3.48 (t, J = 6.5 Hz, 2 H, CH2OBn), 3.42 (dd, J = 11.0, 6.5 Hz, 1 H, CH2OH), 1.65-1.59 (m, 2 H), 1.47-1.34 (m, 4 H), 1.15-1.12 (m, 1 H), 0.91 (d, J = 6.7 Hz, 3 H, CHCH3); 13C NMR (125.7 MHz, CDCl3) d 138.6, 128.2, 127.6, 127.3, 72.9, 70.3, 68.1, 35.7, 32.9, 30.1, 23.6, 14.1; FAB HRMS (NBA) m/e 223.1705, M + H+ calcd for C14H22O2 223.1698.

Synthesis of Silyl Ether 98 as illustrated in Figure 13. Silylation of Alcohol 97. Alcohol 97 (17.0 g, 76.0 mmol) was dissolved in Methylene chloride (350 mL), the solution was cooled to 0 °C and Et3N (21.2 mL, 152.0 mmol, 2.0 equiv) and 4-DMAP (185 mg, 1.52 mmol, 0.05

equiv) were added. After stirring for 5 min, tert-butyldimethylsilyl chloride (17.3 g, 115 mmol, 1.5 equiv) was added portionwise, and the reaction mixture was allowed to stir at 0 °C for 2 h, and then at 25 °C for 10 h. Methanol (20 mL) was added at 0 °C and the solvents were removed under reduced pressure. Ether (200 mL) and saturated aqueous NH4Cl solution (30 mL) were sequentially added, and the organic phase was separated. The aqueous phase was extracted with ether (2 x 100 mL) and the combined organic layer was dried (MgSO4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure silyl ether 98 (24.4 g, 95%): Rf = 0.54 (silica gel, 10% ether in hexanes); [a]22D -2.3 (c 1.1, CHCl3); IR (thin film) nmax 2931, 2860, 1461, 1361, 1249, 1091, 839, 773, 738 cm-1; 1H NMR (500 MHz, CDCl3) d 7.35 (s, 5 H, Ph), 4.51 (s, 2 H, CH2Ph), 3.48 (t, J = 6.5 Hz, 2 H, CH2OBn), 3.43 (dd, J = 10.5, 6.0 Hz, 1 H, CH2OSi), 3.36 (dd, J = 10.5, 6.5 Hz, 1 H, CH2OSi), 1.64-1.60 (m, 3 H), 1.47-1.29 (m, 3 H), 1.15-1.05 (m, 1 H), 0.90 (s, 9 H, SiC(CH3)3), 0.87 (d, J = 6.8 Hz, 3 H, CHCH3), 0.043 (s, 3 H, Si(CH3)2), 0.041 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 138.6, 128.2, 127.5, 127.3, 72.7, 70.3, 68.3, 35.6, 32.9, 30.0, 25.8, 23.5, 18.1, 16.6, -5.5; FAB HRMS (NBA) m/e 337.2553, M + H+ calcd for C20H36O2Si 337.2563.

Synthesis of Alcohol 99 as illustrated in Figure 13. Hydrogenolysis of Benzyl Ether 98. To a solution of

benzyl ether 98 (21.0 g, 62.5 mmol) in THF (200 mL) was added 10% Pd(OH)2/C (1.0 g). The reaction was allowed to proceed under an atmosphere of H2 at a pressure of 50 psi and at 25 °C (Parr hydrogenetor apparatus). After 15 min,

5   no starting benzyl ether was detected by TLC, and the mixture was filtered through celite. The clear solution was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography (silica gel, 40% ether in hexanes) to give alcohol 99 ·

10   (14.7 g, 95%) as a colorless oil: Rf = 0.32 (silica gel, 50% ether in hexanes); [a]22D -3.6 (c 3.6, CHCl3); IR (thin film) nmax 3342, 2931, 2860, 1467, 1384, 1249, 1085, 838, 773, 667 cm-1; 1H NMR (500 MHz, CDCl3) d   3.63 (t, J = 7.0 Hz, 2 H, CH2OH), 3.42 (dd, J = 11.0, 6.0 Hz, 1 H,

15   CH2OSi), 3.35 (dd, J = 11.0, 7.0 Hz, 1 H, CH2OSi), 1.57-1.53 (m, 3 H), 1.42-1.39 (m, 3 H), 1.16-1.06 (m, 1 H), 0.88 (s, 9 H, SiC(CH3)3), 0.85 (d, J = 6.5 Hz, 3 H, CHCH3), 0.03 (s, 3 H, Si(CH3)2), 0.02 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d   68.2, 62.7, 35.6, 32.9,

20   32.8, 25.7, 23.0, 18.2, 16.5, -5.5; FAB HRMS (NBA) m/e 247.2097, M + H+ calcd for C13H30O2Si   247.2093.

Synthesis of Aldehyde 77 as illustrated in Figure 13. Oxidation of Alcohol 99. To a solution of oxalyl

25   chloride (5.6 mL, 65.0 mmol, 2.0 equiv) in Methylene chloride (250 mL) was added dropwise DMSO (9.2 mL, 130 mmol, 4.0 equiv) at -78 °C. After stirring for 15 min, a solution of alcohol 99 (8.0 g, 32.0 mmol, 1.0 equiv) in Methylene chloride (50 mL) was added dropwise at -78 °C

over a 15 min period. The solution was stirred for
further 30 min at -78 °C, and Et3N (27.1 mL, 194 mmol, 6.0
equiv) was added at the same temperature. The reaction
mixture was allowed to warm to 0 °C over 30 min and then
5   ether (400 mL) was added, followed by saturated aqueous
NH4Cl solution (100 mL). The organic phase was separated,
and the aqueous phase was extracted with ether (2 x 300
mL). The combined organic solution was dried (MgSO4),
filtered and concentrated under reduced pressure.
10   Purification by flash column chromatography (silica gel,
20% ether in hexanes) provided aldehyde 77 (7.9 g, 98%) as
a colorless oil: Rf = 0.64 (silica gel, 50% ether in
hexanes); [a]22D -5.1 (c 0.7, CHCl3); IR (thin film) nmax
2952, 2858, 1728, 1466, 1389, 1254, 1095, 841, 776 cm-1;
15   1H NMR (500 MHz, CDCl3) d   9.74 (t, J = 1.5 Hz, 1 H,
CHO), 3.39 (dd, J = 9.8, 6.1 Hz, 1 H, CH2OSi), 3.36 (dd, J
= 9.8, 6.3 Hz, 1 H, CH2OSi), 2.39 (m, 2 H, CH2CHO), 171-
1.64 (m, 1 H), 1.61-1.53 (m, 2 H), 1.44-1.38 (m, 1 H),
1.11-1.05 (m, 1 H), 0.87 (s, 9 H, SiC(CH3)3), 0.85 (d, J =
20   6.5 Hz, 3 H, CHCH3), 0.019 (s, 3 H, Si(CH3)2), 0.004 (s, 3
H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d   202.7, 68.9,
44.1, 35.5, 32.6, 25.8, 23.0, 18.2, 16.5, -5.5; FAB HRMS
(NBA) m/e 245.1932, M + H+ calcd for C13H28O2Si
245.1937.

25

**Synthesis of Alcohol 100 as illustrated in Figure
13.** To a cold (0 °C) solution of aldehyde 77 (7.8 g,
32.0 mmol) in THF (300 mL) was slowly added MeMgBr (1.0 M
solution in THF, 48.0 mL, 48.0 mmol, 1.5 equiv). The

reaction mixture was stirred for 15 min at 0 °C and then
it was diluted with ether (500 mL) and quenched by
carefull addition of saturated aqueous NH4Cl solution (100
mL). The organic phase was washed with brine (100 mL),
dried (MgSO4), and concentrated. The crude product so
obtained was purified by flash column chromatography
(silica gel, 30% ether in hexanes) to give alcohol 100
(7.0 g, 84%) as a colorless oil: Rf = 0.38 (silica gel,
50% ether in hexanes); IR (thin film) nmax 3352, 2931,
2858, 1465, 1384, 1253, 1096, 839, 775 cm-1; 1H NMR (500
MHz, CDCl3) d 3.79 (m, 1 H, CH(CH3)OH), 3.43 (dd, J =
9.8, 6.0 Hz, 1 H, CH2OSi), 3.36 (dd, J = 9.8, 6.8 Hz, 1 H,
CH2OSi), 1.61-1.57 (m, 1 H), 1.47-1.35 (m, 4 H), 1.30-1.26
(m, 1 H), 1.19 (d, J = 6.1 Hz, 3 H, CH(OH)CH3), 1.09-1.05
(m, 1 H), 0.89 (s, 9 H, SiC(CH3)3), 0.86 (d, J = 6.7 Hz, 3
H, CHCH3), 0.04 (s, 6 H, Si(CH3)2); 13C NMR (125.7 MHz,
CDCl3) d 68.2, 67.9, 39.5, 35.6, 33.0, 25.9, 23.4,
23.1, 18.2, 16.6, -5.4; FAB HRMS (NBA) m/e 261.2256, M +
H+ calcd for C14H32O2Si 261.2250.

Synthesis of Ketone 78 as illustrated in Figure 13.
Oxidation of Alcohol 100. To a solution of alcohol 100
(7.0 g, 27.0 mmol) in Methylene chloride (250 mL) was
added molecular sieves (4 Å, 6.0 g) 4-methylmorpholine-N-
oxide (NMO) (4.73 g, 40.0 mmol, 1.5 equiv) and
tetrapropylammonium perruthenate (TPAP) (189 mg, 0.54
mmol, 0.02 equiv) at room temperature. After stirring for
45 min (depletion of starting material, TLC), the reaction
mixture was filtered through celite, and the solvent was

removed under reduced pressure. The crude product was
purified by flash column chromatography (silica gel, 20%
ether in hexanes) to give ketone 78 (6.6 g, 96%) as a
colorless oil: Rf = 0.67 (silica gel, 50% ether in
hexanes); [a]22D -4.5 (c 1.1, CHC13); IR (thin film) nmax
2931, 2849, 1713, 1461, 1355, 1249, 1161, 1091, 838, 773,
667 cm-1; 1H NMR (500 MHz, CDC13) d   3.41 (dd, J = 9.8,
6.0 Hz, 1 H, CH2OSi), 3.36 (dd, J = 9.8, 6.3 Hz, 1 H,
CH2OSi), 2.41 (m, 2 H, CH2COCH3), 2.13 (s, 3 H, COCH3),
168-1.48 (m, 3 H), 1.42-1.35 (m, 1 H), 1.09-1.00 (m, 1 H),
0.88 (s, 9 H, SiC(CH3)3), 0.86 (d, J = 6.7 Hz, 3 H,
CHCH3), 0.03 (s, 6 H, Si(CH3)2); 13C NMR (125.7 MHz,
CDC13) d   209.8, 68.0, 43.9, 35.5, 32.6, 29.7, 25.8,
21.2, 18.2, 16.4, -5.5; FAB HRMS (NBA) m/e 259.2097, M +
H+ calcd for C14H30O2Si 259.2093.

**Synthesis of Iodide 113 as illustrated in Figure
15. Iodination of Alcohol 99.** A solution of alcohol 99
(3.8 g, 15.0 mmol) in ether:MeCN 3:1 (150 mL) was cooled
to 0 °C. Imidazole (3.1 g, 45.0 mmol, 3.0 equiv), Ph3P
(5.9 g, 22.5 mmol, 1.5 equiv) and iodine (5.7 g, 22.5
mmol, 1.5 equiv) were sequentially added and the reaction
mixture was stirred at 0 °C for 0.5 h. A saturated
aqueous solution of Na2S2O3 (200 mL) was added followed
with ether (200 mL). The organic phase was washed with
brine (200 mL), dried (MgSO4) and the solvents were
removed under vacuum. The crude product was purified by
flash column chromatography (silica gel, 10% ether in
hexanes) to give pure iodide 113 (4.9 g, 91%) as a

colorless oil: Rf = 0.68 (silica gel, 10% ether in
hexanes); [a]22D -4.3 (c 1.2, CHCl3); IR (thin film) nmax
2929, 2860, 1461, 1386, 1248, 1090, 836, 774, 664 cm-1; 1H
NMR (500 MHz, CDCl3) d   3.42 (dd, J = 10.0, 6.5 Hz, 1 H,
CH2OSi), 3.38 (dd, J = 10.0, 6.0 Hz, 1 H, CH2OSi), 3.19
(t, J = 7.0 Hz, 2 H, CH2I), 1.85-1.78 (m, 2 H), 1.61-1.55
(m, 1 H), 1.47-1.33 (m, 3 H), 1.10-1.02 (m, 1 H, CH2),
0.89 (s, 9 H, SiC(CH3)3), 0.87 (d, J = 6.7 Hz, 3 H,
CHCH3), 0.04 (s, 6 H, Si(CH3)2); 13C NMR (125.7 MHz,
CDCl3) d   68.1, 35.4, 33.7, 31.8, 27.8, 25.8, 18.2, 16.5,
7.1, -5.5; FAB HRMS (NBA) m/e 229.1983, M - I- calcd for
C13H39IOSi 229.1988.

**Synthesis of Phosphonium Salt 114 as illustrated
in Figure 15.** A mixture of iodide 113 (4.7 g, 13.1
mmol) and Ph3P (3.8 g, 14.4 mmol, 1.1 equiv) was heated
neat at 100 °C for 2 h. Purification by flash column
chromatography (silica gel, Methylene chloride to 7% MeOH
in Methylene chloride) provided phosphonium salt 114 (7.4
g, 91%) as a white solid: Rf = 0.42 (silica gel, 5% MeOH
in Methylene chloride); [a]22D -7.3 (c 1.5, CHCl3); IR
(thin film) nmax 2931, 2849, 1578, 1461, 1431, 1243, 1184,
1102, 997, 914, 838, 720, 685, 532, 503 cm-1; 1H NMR (500
MHz, CDCl3) d   7.82-7.77 (m, 9 H, Ph), 7.74-7.68 (m, 6 H,
Ph), 3.62 (dt, J = 12.5, 8.0 Hz, 2 H, CH2P), 3.34 (dd, J =
9.5, 6.5 Hz, 1 H, CH2OSi), 3.30 (dd, J = 9.5, 6.5 Hz, 1 H,
CH2OSi), 1.69-1.55 (m, 4 H), 1.50-1.46 (m, 1 H), 1.39-1.32
(m, 1 H), 1.10-1.01 (m, 1 H), 0.83 (s, 9 H, SiC(CH3)3),
0.79 (d, J = 6.6 Hz, 3 H, CHCH3), -0.04 (s, 6 H,

Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d   135.0, 133.6,
133.5, 133.2, 130.5, 130.4, 68.0, 35.2, 32.4, 27.8, 25.8,
23.2, 22.7, 18.2, 16.4, -5.5.

5   Synthesis of Olefin 101 as illustrated in Figure
15. Method A. From Phosphonium Salt 79 and Aldehyde 77.
Phosphonium salt 79 (13.60 g, 19.4 mmol, 1.2 equiv) was
dissolved in THF (80 mL, 0.2 M) and the solution was
cooled to 0 °C. Sodium hexamethyldisilylamide (NaHMDS,
10   19.4 mL, 19.4 mmol, 1.0 M solution in THF, 1.2 equiv) was
slowly added and the resulting mixture was stirred for 15
min before aldehyde 77 (3.96 g, 16.2 mmol, 1.0 equiv, in
10 mL of THF) was added at the same temperature. Stirring
was continued for another 15 min at 0 °C and then, the
15   reaction mixture was quenched with saturated aqueous NH4Cl
solution (25 mL). Ether (250 mL) was added and the
organic phase was separated and washed with brine (2 x 40
mL), dried (MgSO4) and concentrated under vacuo. The
crude product was purified by flash column chromatography
20   (silica gel, 10% ether in hexane) to afford olefin 34
(6.70 g, 77%) as a mixture of Z- and E-isomers (ca 9 : 1
by 1H NMR). Method B. From Phosphonium Salt 114 and
Aldehyde 82. Phosphonium salt 114 (7.40 g, 11.96 mmol,
1.2 equiv) was dissolved in THF (120 mL, 0.1 M) and the
25   solution was cooled to 0 °C. Sodium
hexamethyldisilylamide (NaHMDS, 11.96 mL, 11.96 mmol, 1.0
M solution in THF, 1.2 equiv) was slowly added at the same
temperature and the resulting mixture was stirred for 15
min, before aldehyde 82 (3.20 g, 9.83 mmol, 1.0 equiv, in

20 mL of THF; vida supra) was slowly added. Stirring was continued for another 15 min at 0 °C and then the mixture was quenched with saturated aqueous NH4Cl solution (150 mL). Ether (200 mL) was added and the organic phase was separated and washed with brine (2 x 150 mL), dried (MgSO4) and concentrated under reduced pressure to afford the crude product. Flash column chromatography (silica gel, 10% ether in hexane) furnished olefin 101 (3.65 g, 69% yield) as a mixture of Z- and E-isomers (ca 9:1 by 1H NMR): Rf = 0.75 (silica gel, 50% ether in hexane); [a]22D +4.0 (c 0.5, CHCl3); IR (thin film) nmax 2930, 2856, 1465, 1388, 1253, 1089, 939, 838 cm-1; 1H NMR (500 MHz, CDCl3) (signals for the Z-isomer (34) only reported) d 6.92 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH3), 5.49-5.31 (m, 2 H, CH=CH), 4.12 (dd, J = 6.5, 6.4 Hz, 1 H, CHOSi), 3.44 (dd, J = 9.8, 5.8 Hz, 1 H, CH2OSi), 3.34 (dd, J = 9.8, 6.8 Hz, 1 H, CH2OSi), 2.71 (s, 3 H, N=C(S)CH3), 2.39-2.24 (m, 2 H, CH2CHOSi), 2.00 (s, 3 H, CH=CCH3), 2.05-1.96 (m, 2 H), 1.59-1.51 (m, 1 H), 1.42-1.23 (m, 3 H), 1.10-0.98 (m, 1 H), 0.89 (s, 18 H, SiC(CH3)3), 0.85 (d, J = 6.8 Hz, 3 H, CH3CH), 0.06 (s, 3 H, Si(CH3)2), 0.04 (s, 6 H, Si(CH3)2), 0.01 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 164.3, 153.1, 142.2, 131.4, 125.7, 118.8, 114.9, 78.7, 68.3, 35.7, 34.6, 32.9, 27.8, 27.1, 25.9, 25.8, 19.2, 18.3, 18.2, 16.7, 13.9, -4.7, -4.9, -5.4; FAB HRMS (NBA) m/e 538.3582, M + H+ calcd for C29H55NO2SSi2 538.3570.

Synthesis of alcohol 102 as illustrated in Figure 14. Compound 101 (1.77 g, 3.29 mmol) was dissolved in

Methylene chloride : MeOH (1:1, 66 mL) and the solution
was cooled to 0 °C and CSA (764 mg, 3.29 mmol, 1.0 equiv)
was added over a 5 min period. The mixture was stirred
for 30 min at 0 °C, and then for 1 h at 25 °C. Et3N (2.0
mL) was added, and the solvents were removed under reduced
pressure. Flash column chromatography (silica gel, 50%
ether in hexanes) furnished the desired alcohol 35 (1.2 g,
86%): Rf = 0.72 (silica gel, 80% ether in hexanes); [a]22D
+1.1 (c 1.0, CHCl3); IR (thin film) nmax 3370, 2923, 2857,
1464, 1384, 1253, 1185, 1074, 836, 776 cm-1; 1H NMR (500
MHz, CDCl3) d   6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H,
CH=CCH3), 5.45-5.32 (m, 2 H, CH=CH), 4.12 (dd, J = 6.5,
6.4 Hz, 1 H, CHOSi), 3.46 (dd, J = 10.5, 5.9 Hz, 1 H,
CH2OH), 3.37 (dd, J = 10.5, 6.5 Hz, 1 H, CH2OH), 2.68 (s,
3 H, N=C(S)CH3), 2.39-2.21 (m, 2 H, CH2CHOSi), 2.21 (s, 1
H, OH), 1.98 (s, 3 H, CH=CCH3), 2.05-1.95 (m, 2 H), 1.59-
1.51 (m, 1 H), 1.42-1.23 (m, 3 H), 1.10-0.98 (m, 1 H),
0.88 (d, J = 6.5 Hz, 3 H, CH3CH), 0.87 (s, 9 H,
SiC(CH3)3), 0.05 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H,
Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 164.4, 152.9,
142.2, 131.2, 125.8, 118.7, 114.8, 78.6, 67.9, 35.5, 34.6,
32.7, 27.5, 26.9, 25.8, 25.7, 18.9, 16.5, 13.7, -4.8, -
5.1; FAB HRMS (NBA/NaI) m/e 446.2534, M + Na+ calcd for
C23H41NO2SSi 446.2525.

**Synthesis of Aldehyde 74 as illustrated in Figure
14.** Oxidation of Alcohol 102. Alcohol 102 (1.9 g, 4.5
mmol) was dissolved in Methylene chloride (45 mL, 0.1 M).
DMSO (13.5 mL), Et3N (3.0 mL, 22.4 mmol, 5.0 equiv) and

SO3·pyr (1.43 g, 8.98 mmol, 2.0 equiv) were added at 25 °C
and the resulting mixture was stirred for 30 min.
Saturated aqueous NH4Cl solution (100 mL) and ether (200
mL) were added sequentially. The organic phase was washed
with brine (2 x 30 mL), dried (MgSO4) and the solvents
were removed under reduced pressure. Flash column
chromatography (silica gel, 30% ether in hexanes)
furnished aldehyde 74 (1.79 g, 94%): Rf = 0.55 (silica
gel, 40% ether in hexanes); [a]22D +13.3 (c 0.7, CHCl3);
IR (thin film) nmax 2930, 2856, 1725, 1504, 1462, 1385,
1253, 1182, 1076, 938, 836, 776 cm-1; 1H NMR (600 MHz,
CDCl3) d   9.57, (d, J = 1.8 Hz, 1 H, CHO), 6.91 (s, 1 H,
SCH=C), 6.44 (s, 1 H, CH=CCH3), 5.45-5.35 (m, 2 H, CH=CH),
4.11 (dd, J = 6.6, 6.3 Hz, 1 H, CHOSi), 2.69 (s, 3 H,
N=C(S)CH3), 2.34-2.24 (m, 3 H), 2.05-2.01 (m, 2 H), 1.98
(s, 3 H, CH=CCH3), 1.71-1.64 (m, 1 H), 1.41-1.29 (m, 3 H),
1.05 (d, J = 7.0 Hz, 3 H, CH3CH), 0.87 (s, 9 H,
SiC(CH3)3), 0.04 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H,
Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d   205.2, 164.4,
153.0, 142.0, 130.6, 126.4, 118.8, 115.0, 78.7, 46.2,
34.7, 30.0, 27.3, 26.9, 25.8, 19.2, 18.2, 13.9, 13.2, -
4.7, -5.0; FAB HRMS (NBA) m/e 422.2559, M + H+ calcd for
C23H39NO2SSi   422.2549.

**Synthesis of compounds 105 and 106 as illustrated
in Figure 14:** Aldol Reaction of Keto Acid 76 with
Aldehyde 74. A solution of keto acid 76 (1.52 g, 5.10
mmol, 1.2 equiv; synthesized vida supra) in THF (10 mL)
was added dropwise to a freshly prepared solution of LDA

[diisopropylamine (1.78 mL, 12.78 mmol) was added to n-BuLi (7.95 mL, 1.6 M solution in hexanes, 12.78 mmol) in 20 mL of THF at 0 °C] at -78 °C. After stirring for 15 min, the solution was allowed to warm to -40 °C, and after 0.5 h at that temperature it was recooled to -78 °C. A solution of aldehyde 74 (1.79 g, 4.24 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred for 15 min, and then quenched at -78 °C by slow addition of saturated aqueous NH4Cl solution (20 mL). The reaction mixture was warmed to 0 °C, and AcOH (2.03 mL, 26.84 mmol, 6.3 equiv) was added, followed by addition of EtOAc (50 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic solution was dried over MgSO4 and concentrated under vacuum to afford a mixture of aldol products 103a:103b in a ca 1:1 ratio (1H NMR) and unreacted keto acid 76. The mixture was dissolved in Methylene chloride (50 mL) and treated, at 0 °C, with 2,6-lutidine (3.2 mL, 27.36 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (4.2 mL, 18.24 mmol). After stirring for 2 h (complete reaction by TLC), aqueous HCl (20 mL, 10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with Methylene chloride (3 x 20 mL) and the combined organic solution was washed with brine (50 mL), dried (MgSO4) and concentrated under reduced pressure to give a mixture of the tetra-tert-butyldimethylsilyl ethers 104a and 104b. The crude product was dissolved in MeOH (50 mL) and K2CO3 (1.40 g, 10.20 mmol) was added at 25 °C. The

reaction mixture was vigorously stirred for 15 min, and
then filtered. The residue was washed with MeOH (20 mL)
and the solution was acidified with ion exchange resin
(DOWEX 50WX8-200) to pH 4-5, and filtered again. The
solvent was removed under reduced pressure and the
resulting residue was dissolved in EtOAc (50 mL) and
washed with saturated aqueous NH_4Cl solution (50 mL). The
aqueous phase was extracted with EtOAc (4 x 25 mL) and the
combined organic solution was dried ($MgSO_4$), filtered and
concentrated to furnish a mixture of carboxylic acids 105,
106 and 76. Purification by preparative thin layer
chromatography (silica gel, 5% MeOH in Methylene
chloride), gave pure acids 105 (1.1 g, 31% from 7) and 106
(1.0 g, 30% from 7) as colorless oils. 38: R_f = 0.61
(silica gel, 5% MeOH in Methylene chloride); $[a]_{22}^D$ -8.8
(c 0.8, $CHCl_3$); IR (thin film) nmax 2931, 2856, 1712,
1466, 1254, 1083, 836 cm-1; ^1H NMR (600 MHz, $CDCl_3$) d
6.94 (s, 1 H, SCH=C), 6.61 (s, 1 H, $CH=CCH_3$), 5.44-5.41
(m, 2 H, CH=CH), 4.40 (dd, J = 6.5, 3.2 Hz, 1 H,
$(CH_3)_2CCHOSi$), 4.11 (dd, J = 6.5, 5.9 Hz, 1 H,
CH_2CHOSi), 3.75 (dd, J = 6.5, 3.0 Hz, 1 H, $CH(CH_3)CHOSi$),
3.12 (dq, J = 7.0, 6.5 Hz, 1 H, $C(O)CH(CH_3)$), 2.69 (s, 3
H, $N=C(CH_3)S$), 2.48 (dd, J = 16.0, 3.2 Hz, 1 H, CH_2COOH),
2.35 (dd, J = 16.0, 6.7 Hz, 1 H, CH_2COOH), 2.39-2.28 (m, 2
H, $CH_2CH=CH$), 2.10-1.92 (m, 2 H, CH=CHCH_2), 1.95 (s, 3 H,
$CH=C(CH_3)$), 1.42-1.30 (m, 5 H, $CH(CH_3)$, 2 x CH_2), 1.18 (s,
3 H, $C(CH_3)_2$), 1.10 (s, 3 H, $C(CH_3)_2$), 1.06 (d, J = 7.0
Hz, 3 H, $CH(CH_3)$), 0.90-0.85 (m, 30 H, $CH(CH_3)$, 3 x
$SiC(CH_3)_3$), 0.12 (s, 3 H, $Si(CH_3)_2$), 0.09 (s, 3 H,

Si(CH3)2), 0.07 (s, 3 H, Si(CH3)2), 0.05 (s, 3 H, Si(CH3)2), 0.04 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 218.1, 176.7, 164.8, 152.8, 142.6, 131.3, 125.9, 118.6, 114.7, 78.6, 77.4, 73.4, 53.5, 44.9, 40.1, 38.8, 34.6, 30.7, 28.0, 27.8, 26.2, 26.0, 25.8, 23.6, 19.1, 18.8, 18.5, 18.2, 17.4, 15.7, 13.8, -3.7, -3.8, -4.2, -4.6, -4.7, -4.9; FAB HRMS (NBA/CsI) m/e 970.4318, M + Cs+ calcd for C44H83NO6SSi3 970.4303. 39: Rf = 0.70 (silica gel, 5% MeOH in Methylene chloride); [a]22D +2.2 (c 3.5, CHCl3); IR (thin film) nmax 2929, 2856, 1713, 1470, 1386, 1254, 1082, 988, 836, 776 cm-1; 1H NMR (600 MHz, CDCl3) d 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH3), 5.44-5.38 (m, 1 H, CH=CH), 5.37-5.32 (m, 1 H, CH=CH), 4.55 (dd, J = 6.7, 3.7 Hz, 1 H, (CH3)2CCHOSi), 4.11 (dd, J = 6.7, 6.2 Hz, 1 H, CH2CHOSi), 3.83 (d, J = 8.4, 1 H, CH(CH3)CHOSi), 3.09 (dq, J = 7.0, 6.9 Hz, 1 H, C(O)CH(CH3)), 2.73 (s, 3 H, N=C(CH3)S), 2.40 (dd, J = 16.3, 3.8 Hz, 1 H, CH2COOH), 2.35-2.22 (m, 3 H, CH2COOH, CH2CH=CH), 1.98-1.94 (m, 2 H, CH=CHCH2), 1.92 (s, 3 H, CH=C(CH3)), 1.34-1.21 (m, 5 H, CH(CH3), 2 x CH2), 1.18 (s, 3 H, C(CH3)2), 1.07 (s, 3 H, C(CH3)2), 1.05 (d, J = 7.0 Hz, 3 H, CH(CH3)), 0.89 (s, 9 H, SiC(CH3)3), 0.88 (s, 9 H, SiC(CH3)3), 0.85 (s, 9 H, SiC(CH3)3), 0.82 (d, J = 6.9 Hz, 3 H, CH(CH3)), 0.07 (s, 6 H, 2 x Si(CH3)2), 0.06 (s, 3 H, Si(CH3)2), 0.05 (s, 3 H, Si(CH3)2), 0.04 (s, 3 H, Si(CH3)2), 0.01 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 217.7, 175.3, 165.4, 152.4, 143.1, 131.3, 125.9, 118.3, 114.6, 78.6, 76.7, 72.3, 53.8, 45.7, 40.1, 37.9, 34.9, 34.6, 27.7,

27.3, 26.3, 26.2, 26.0, 25.8, 22.4, 19.0, 18.6, 18.2, 18.1, 16.8, 13.9, 13.5, -3.4, -3.6, -4.3, -4.6, -4.7, -4.9; FAB HRMS (NBA/CsI) m/e 970.4331, M + Cs+ calcd for $C_{44}H_{83}NO_6SSi_3$ 970.4303.

Synthesis of Hydroxy Acid 72 as illustrated in Figure 14. Selective Desilylation of tris(Silyl) Ether 105. A solution of tris(silyl) ether 105 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO4) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in Methylene chloride) to provide hydroxy acid 72 (203 mg, 78%) as a yellow oil: Rf = 0.40 (silica gel, 5% MeOH in Methylene chloride); [a]22D -19.2 (c 0.1, CHC13); IR (thin film) nmax 3358, 2932, 2857, 1701, 1466, 1254, 1088, 988, 835 cm-1; 1H NMR (600 MHz, CDC13) d 6.95 (s, 1 H SCH=C), 6.67 (s, 1 H, CH=CCH3), 5.58-5.54 (m, 1 H, CH=CH), 5.43-5.39 (m, 1 H, CH=CH), 4.39 (dd, J = 6.7, 3.9 Hz, 1 H, (CH3)2CCHOSi), 4.18 (dd, J = 7.5, 5.0 Hz, 1 H, CH2CHOH), 3.78 (dd, J = 6.9, 1.0 Hz, 1 H, CH(CH3)CHOSi), 3.11 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)CHCH3), 2.70 (s, 3 H, N=C(CH3)S), 2.43 (dd, J = 16.2, 3.9 Hz, 1 H, CH2COOH), 2.40-2.35 (m, 2 H, CH2CH=CH), 2.35 (dd, J = 16.2, 6.7 Hz, 1 H, CH2COOH), 2.15-2.10 (m, 1 H,

CH=CHCH2), 2.00 (s, 3 H, CH=C(CH3)), 1.99-1.95 (m, 1 H,
CH=CHCH2), 1.48-1.30 (m, 5 H, CH(CH3), 2 x CH2), 1.18 (s,
3 H, C(CH3)2), 1.08 (s, 3 H, C(CH3)2), 1.05 (d, J = 6.7
Hz, 3 H, CH(CH3)), 0.89-0.84 (m, 21 H, CH(CH3),
SiC(CH3)3), 0.09 (s, 3 H, Si(CH3)2), 0.05 (s, 3 H,
Si(CH3)2), 0.04 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H,
Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d   218.9, 175.4,
166.3, 152.8, 143.5, 134.4, 125.7, 119.5, 115.9, 74.4,
54.7, 45.5, 40.9, 40.0, 34.3, 31.9, 30.6, 28.9, 28.8,
27.0, 26.8, 26.7, 24.4, 20.0, 19.6, 19.3, 19.1, 17.9,
17.1, 15.5, -2.9, -3.1, -3.3, -3.8; FAB HRMS (NBA/CsI) m/e
856.3459, M + Cs+ calcd for C38H69NO6SSi2   856.3439.

**Synthesis of Hydroxy Acid 107 as illustrated in
Figure 14.**   Selective Desilylation of tris(Silyl) Ether
106.   Carboxylic acid 106 (150 mg, 0.18 mmol) was
converted to hydroxy acid 107 (107 mg, 82%) according to
the procedure described above for 72.   107: Yellow oil; Rf
= 0.45 (silica gel, 5% MeOH in Methylene chloride); [a]22D
-8.0 (c 0.2, CHCl3); IR (thin film) nmax 3225, 2943, 2860,
1719, 1690, 1461, 1384, 1296, 1250, 1190, 1085, 985, 832,
761, 667 cm-1; 1H NMR (600 MHz, CDCl3) d   6.93 (s, 1 H
SCH=C), 6.60 (s, 1 H, CH=CCH3), 5.54-5.50 (m, 1 H, CH=CH),
5.40-5.34 (m, 1 H, CH=CH), 4.54 (dd, J = 6.4, 3.7 Hz, 1
H, (CH3)2CCHOSi), 4.15 (dd, J = 6.5, 6.3 Hz, 1 H,
CH2CHOH), 3.82 (d, J = 7.6 Hz, 1 H, CH(CH3)CHOSi), 3.09
(dq, J = 6.9, 6.5 Hz, 1 H, C(O)CHCH3), 2.71 (s, 3 H,
N=C(CH3)S), 2.37-2.32 (m, 3 H, CH2CH=CH, CH2COOH), 2.30
(dd, J = 16.3, 6.4 Hz, 1 H, CH2COOH), 2.15-2.10 (m, 2 H,

CH=CHCH2), 1.97 (s, 3 H, CH=C(CH3)), 1.36-1.18 (m, 5 H, CH(CH3), 2 x CH2), 1.17 (s, 3 H, C(CH3)2), 1.07 (s, 3 H, C(CH3)2), 1.05 (d, J = 6.8 Hz, 3 H, CH(CH3)), 0.88 (s, 9 H, SiC(CH3)3), 0.85-0.82 (m, 12 H, CH(CH3), SiC(CH3)3), 0.07 (s, 3 H, Si(CH3)2), 0.06 (s, 3 H, Si(CH3)2), 0.05 (s, 6 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 218.2, 175.4, 165.4, 152.2, 142.0, 133.1, 124.9, 118.6, 115.1, 74.4, 53.8, 45.8, 40.2, 38.9, 37.7, 34.8, 33.2, 27.9, 27.5, 27.1, 26.2, 26.1, 26.0, 22.6, 21.4, 18.8, 18.6, 16.9, 14.5, 13.3, -3.4, -3.6, -4.3, -4.6; FAB HRMS (NBA/CsI) m/e 856.3402, M + Cs+ calcd for $C_{38}H_{69}NO_6SSi_2$ 856.3439.

Synthesis of Lactone 108 as illustrated in Figure 14. Macrolactonization of Hydroxy Acid 72. A solution of hydroxy acid 72 (200 mg, 0.28 mmol) in THF (4 mL) was treated at 0 °C with Et3N (0.23 mL, 1.68 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.40 mmol, 5.0 equiv). The reaction mixture was stirred at 0 °C for 15 min, and then added to a solution of 4-DMAP (342 mg, 2.80 mmol, 10.0 equiv) in toluene (140 mL) at 25 °C and stirred at that temperature for 0.5 h. The reaction mixture was concentrated under reduced pressure to a small volume and filtered through silica gel. The residue was washed with 40% ether in hexanes, and the resulting solution was concentrated. Purification by flash column chromatography (silica gel, 2% MeOH in Methylene chloride) furnished lactone 108 (178 mg, 90%) as a colorless oil: Rf = 0.37 (silica gel, 30% ether in hexanes); [a]22D -22.5

(c 0.3, CHCl3); IR (thin film) nmax 2925, 2854, 1734, 1693, 1464, 1381, 1252, 1187, 1158, 1099, 988, 829, 758 cm-1; 1H NMR (600 MHz, CDCl3) d 6.98 (s, 1 H, SCH=C), 6.58 (s, 1 H, CH=CCH3), 5.53 (m, 1 H, CH=CH), 5.43-5.34 (m, 1 H, CH=CH), 5.00 (d, J = 10.2 Hz, 1 H, O=COCH), 4.03 (d, J = 10.5 Hz, 1 H, CHOSi), 3.89 (d, J = 9.0 Hz, 1 H, CHOSi), 2.98 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)CHCH3), 2.85 (d, J = 16.7 Hz, 1 H, CH2COO), 2.72 (s, 3 H, N=C(CH3)S), 2.66 (dd, J = 16.7, 10.7 Hz, 1 H, CH2COO), 2.40-2.30 (m, 1 H, CH=CHCH2), 2.11 (s, 3 H, CH=C(CH3)), 2.10-2.04 (m, 2 H, CH2CH=CH), 1.92-1.83 (m, 1 H, CH=CHCH2), 1.66-1.38 (m, 5 H, CH(CH3), 2 x CH2), 1.17 (s, 3 H, C(CH3)2), 1.13 (s, 3 H, C(CH3)2), 1.06 (d, J = 7.0 Hz, 3 H, CH(CH3)), 0.94 (d, J = 7.0 Hz, 3 H, CH(CH3)), 0.92 (s, 9 H, SiC(CH3)3), 0.83 (s, 9 H, SiC(CH3)3), 0.09 (s, 3 H, Si(CH3)2), 0.07 (s, 3 H, Si(CH3)2), 0.05 (s, 3 H, Si(CH3)2), -0.12 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 215.0, 171.3, 165.4, 135.7, 135.1, 125.8, 122.7, 119.9, 115.9, 79.5, 76.4, 53.3, 48.0, 38.8, 31.7, 31.3, 29.7, 29.2, 28.4, 26.4, 26.2, 26.1, 25.9, 24.2, 19.1, 18.7, 18.6, 17.7, 15.3, -3.1, -3.2, -3.7, -5.8; FAB HRMS (NBA) m/e 706.4382, M + H+ calcd for C38H67NO5SSi2 706.4357.

Synthesis of Lactone 109 as illustrated in Figure 14. Macrolactonization of Hydroxy Acid 107. The cyclization of hydroxy acid 107 (100 mg, 0.14 mmol) was carried out exactly as described for 108 above and yielded lactone 109 (84 mg, 85%) as a colorless oil: Rf = 0.40 (silica gel, 30% ether in hexanes); [a]22D -40.5 (c 0.2,

CHC13); IR (thin film) nmax 2929, 2855, 1739, 1690, 1469, 1384, 1253, 1180, 1089, 1053, 985, 835, 775 cm-1; 1H NMR (600 MHz, CDC13) d 6.94 (s, 1 H, SCH=C), 6.53 (s, 1 H, CH=CCH3), 5.55-5.46 (m, 1 H, CH=CH), 5.39-5.30 (m, 1 H, CH=CH), 5.32 (dd, J = 7.0, 3.0 Hz, 1 H, O=COCH), 4.43 (dd, J = 7.5, 2.9 Hz, 1 H, CHOSi), 3.99 (d, J = 7.1 Hz, 1 H, CHOSi), 3.20 (dq, J = 7.3, 7.1 Hz, 1 H, C(O)CHCH3), 2.71 (s, 3 H, N=C(CH3)S), 2.59 (m, 1 H, CH=CHCH2), 2.21 (dd, J = 14.6, 3.2 Hz, 1 H, CH2COO), 2.20 (dd, J = 14.6, 7.6 Hz, 1 H, CH2COO), 2.16 (s, 3 H, CH=C(CH3)), 2.15-1.95 (m, 3 H, CH=CHCH2, CH2CH=CH), 1.60-1.50 (m, 3 H, CH(CH3), 2 x CH2), 1.47-1.35 (m, 2 H, CH(CH3), 2 x CH2), 1.24 (s, 3 H, C(CH3)2), 1.11 (d, J = 7.2 Hz, 3 H, CH(CH3)), 1.09 (s, 3 H, C(CH3)2), 0.90 (s, 9 H, SiC(CH3)3), 0.86 (s, 9 H, SiC(CH3)3), 0.83 (d, J = 6.7 Hz, 3 H, CH(CH3)), 0.09 (s, 6 H, 2 x Si(CH3)2), 0.01 (s, 3 H, Si(CH3)2), -0.05 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDC13) d 221.2, 171.6, 165.8, 134.9, 134.1, 125.7, 125.2, 120.7, 117.1, 78.8, 75.2, 74.5, 54.3, 48.1, 42.5, 37.9, 33.7, 32.4, 26.8, 26.7, 26.5, 26.2, 25.8, 19.7, 19.2, 19.0, 18.8, 17.7, 15.9, 14.1, -3.0, -3.3, -3.7, -4.3; FAB HRMS (NBA) m/e 706.4333, M + H+ calcd for C38H67NO5SSi2 706.4357.

Synthesis of Dihydroxy Lactone 70 as illustrated in Figure 14. To lactone 108 (50 mg, 0.071 mmol), cooled to -20 °C, was added a freshly prepared 20% (v/v) CF3COOH solution in Methylene chloride (400 mL). The reaction mixture was allowed to reach 0 °C and was stirred for 1 h at that temperature. The solvents were evaporated

under reduced pressure and the crude product was purified
by preparative thin layer chromatography (silica gel, 6%
MeOH in Methylene chloride) to afford pure dihydroxy
lactone 70 (31 mg, 92%): Rf = 0.38 (silica gel, 5% MeOH in
Methylene chloride); [a]22D -80.2 (c 1.7, CHCl3); IR (thin
film) nmax 3470, 2929, 1733, 1686, 1464, 1380, 1250, 1182,
1045, 978, 732 cm-1; 1H NMR (500 MHz, C6D6) d   6.83 (s, 1
H, SCH=C), 6.56 (s, 1 H, CH=CCH3), 5.48 (dd, J = 7.0, 3.0
Hz, 1 H, O=COCH), 5.43-5.41 (m, 2 H, CH=CH), 4.21 (d, J
= 11.5 Hz, 1 H, CHOH), 3.77 (bs, 1 H, CHOH), 3.13 (bs, 1
H, OH), 3.01 (bs, 1 H, OH), 2.95 (m, 1 H, C(O)CHCH3),
2.70-2.62 (m, 1 H, CH2COO), 2.47 (ddd, J = 14.6, 11.5 Hz,
1 H, CH2COO), 2.27 (s, 3 H, N=C(CH3)S), 2.18-2.12 (m, 2 H,
CH=CHCH2), 2.15 (s, 3 H, CH=C(CH3)), 1.97-1.83 (m, 2H,
CH2CH=CH), 1.56-1.50 (m, 1 H, CH(CH3)), 1.41-1.22 (m, 4 H,
2 x CH2), 1.15 (d, J = 7.0 Hz, 3 H, CH(CH3)), 1.07 (d, J
= 6.0 Hz, 3 H, CH(CH3)), 1.07 (s, 3 H, C(CH3)2), 1.06 (s,
3 H, C(CH3)2); 13C NMR (150.9 MHz, C6D6) d 220.2, 170.6,
165.4, 153.8, 139.2, 134.1, 126.1, 120.4, 116.9, 79.2,
74.9, 73.2, 54.2, 42.5, 40.3, 39.5, 32.9, 32.6, 28.6,
28.4, 23.3, 19.3, 19.1, 16.4, 16.3, 14.4; FAB HRMS
(NBA/CsI) m/e 610.1580, M + Cs+ calcd for C26H39NO5S
610.1603.

**Synthesis of Dihydroxy Lactone 110 as illustrated
in Figure 14.** Lactone 109 (38.0 mg, 0.054 mmol) was
treated with CF3COOH in exactly the same way as described
above for 70, yielding dihydroxy lactone 110 (24.5 mg,
95%): Rf = 0.30 (silica gel, 6% MeOH in Methylene

chloride); [a]22D -93.1 (c 0.1, CHC13); IR (thin film)
nmax 3450, 2929, 1735, 1685, 1464, 1380, 1250, 1182, 1045,
978, 732 cm-1; 1H NMR (600 MHz, CDC13) d 6.96 (s, 1 H,
SCH=C), 6.51 (s, 1 H, CH=CCH3), 5.60-5.50 (m, 2 H, CH=CH),
5.40-5.32 (m, 1 H, O=COCH), 4.25 (d, J = 9.5 Hz, 1 H,
CHOH), 3.55 (d, J = 9.6 Hz, 1 H, CHOH), 3.39 (bs, 1 H,
OH), 3.31 (dq, J = 6.9, 6.7 Hz, 1 H, C(O)CHCH3), 2.99
(bs, 1 H, OH), 2.71 (s, 3 H, N=C(CH3)S), 2.69-2.61 (m, 1
H, CH=CHCH2), 2.59 (d, J = 16.3 Hz, 1 H, CH2COO), 2.45-
2.35 (m, 2 H, CH2COO, CH=CHCH2), 2.20-2.10 (m, 1 H,
CH2CH=CH), 2.08 (s, 3 H, CH=C(CH3)), 1.98-1.90 (m, 1 H,
CH2CH=CH), 1.59-1.50 (m, 1 H, CH(CH3)), 1.49-1.30 (m, 4 H,
2 x CH2), 1.17 (s, 3 H, C(CH3)2), 1.11 (d, J = 6.9 Hz, 3
H, CH(CH3)), 1.03 (s, 3 H, C(CH3)2), 1.01 (d, J = 7.0 Hz,
3 H, CH(CH3)); 13C NMR (150.9 MHz, CDC13) d 222.2, 171.1,
165.2, 153.5, 139.5, 133.2, 125.1, 120.0, 116.7, 78.4,
74.1, 72.9, 52.5, 40.7, 39.5, 37.9, 34.5, 32.7, 31.3,
27.6, 24.7, 22.2, 18.9, 17.5, 15.5, 15.3; FAB HRMS (NBA)
m/e 478.2610, M + H+ calcd for C26H39NO5S 478.2627.
**Synthesis of Epothilone A (1) as illustrated in
Figure 14.** Epoxidation of Lactone 70 with
Methyl(trifluoromethyl)dioxirane. To a solution of 70 (10
mg, 21.0 mmol) in MeCN (200 mL) was added 4.10 - 4.00 M
aqueous solution of disodium ethylenediaminetetraacetate
(Na2EDTA, 120 mL; Aldrich) and the reaction mixture was
cooled to 0 'C. 1,1,1-Trifluoroacetone (200 mL) was added
followed by a mixture of Oxone® (61 mg, 0.10 mmol, 5.0
equiv) and NaHCO3 (14.0 mg, 0.17 mmol, 8.0 equiv) with
stirring until completion of the reaction was revealed by

TLC. The reaction mixture was treated with excess Me2S (100 mL) and water (500 mL) and was then extracted with EtOAc (4 x 2 mL). The combined organic phase was dried (MgSO4), filtered, and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) gave a mixture of epothilones A (1) and its α-epoxide epimer (8.6 mg, 78% total yield). A second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnished pure epothilone A (1) (6.4 mg, 65%) as a white solid.. 1: Rf = 0.23 (silica gel, 5% MeOH in Methylene chloride); [a]22D -45.0 (c 0.02, MeOH); IR (thin film) nmax 3476, 2974, 1738, 1692 cm-1; 1H NMR (600 MHz, C6D6) d 6.71 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH3), 5.45 (dd, J = 8.2, 2.3 Hz, 1 H, O=COCH), 4.15 (dd, J = 10.8, 2.9 Hz, 1 H, CHOH), 3.81-3.78 (m, 1 H, CHOH), 3.65 (bs, 1 H, OH), 3.03 (dq, J = 6.9, 6.5 Hz, 1 H, C(O)CHCH3), 2.77 (ddd, J = 7.9, 4.0, 4.0 Hz, 1 H, CH2CHO), 2.62-2.58 (m, 1 H, CH2CHO), 2.40 (dd, J = 14.4, 10.8 H 1 H, CH2COO), 2.26 (bs, 1 H, OH), 2.21 (s, 3 H, N=C(CH3)S), 2.19 (dd, J = 14.4, 2.9 Hz, 1 H, CH2COO), 2.05 (s, 3 H, CH=C(CH3)), 1.86 (ddd, J = 15.2, 2.5, 2.5 Hz, 1 H, CH2CHO), 1.81-1.74 (m, 1 H, CH2CHO), 1.68 (ddd, J = 15.2, 7.6, 7.6 Hz, 1 H, CH2CHO), 1.53-1.49 (m, 1 H, CH2CHO), 1.40-1.15 (m, 5 H, CH(CH3), 2 x CH2), 1.06 (d, J = 7.0 Hz, 3 H, CH(CH3)), 1.03 (s, 3 H, C(CH3)2), 0.97 (s, 3 H, C(CH3)2), 0.95 (d, J = 6.9 Hz, 3 H, CH(CH3)); 13C NMR (150.9 MHz, C6D6) d 219.0, 170.2, 164.7, 153.0, 137.5, 119.9, 116.6, 76.6, 75.2, 73.5, 57.2, 54.2, 52.9, 43.8, 39.1, 36.3, 31.7, 30.3, 27.3, 23.9, 21.1, 20.6,

18.7, 17.4, 15.7, 14.6; HRMS (FAB), calcd for C26H39CsNO6S
(M + Cs+) 626.1552, found 626.1531.

**Synthesis of 6S,7R-Epothilones 111 and 112 as
illustrated in Figure 14.** Epoxidation of Lactone 110.
To a solution of lactone 110 (9.0 mg, 18.8 mmol) in MeCN
(0.5 mL) was added disodium ethylenediaminetetraacetate
(Na2EDTA, 4.10-4 M aqueous solution, 200 mL) and 1,1,1-
trifluoroacetone (200 mL) at 0 °C. The resulting solution
was stirred at 0 °C while a mixture of solid Oxone® (58
mg, 94.0 mmol, 5.0 equiv) and NaHCO3 (14.0 mg, 0.17 mmol,
8.8 equiv) was added portionwise until completion of the
reaction was established by TLC). The reaction mixture
was treated with excess Me2S (100 mL) and water (500 mL)
and was extracted with EtOAc (4 x 2 mL). The combined
organic phase was dried (MgSO4), filtered, and
concentrated. Purification by preparative thin layer
chromatography (silica gel, 5% MeOH in Methylene chloride)
gave a mixture of epothilones 111 and 112 (8.1 mg, 87%
total yield, ca 2:1 ratio by 1H NMR). The major
diastereoisomer (111, stereochemistry unassigned) was
isolated by preparative thin layer chromatography (silica
gel, 70% EtOAc in hexanes) (5.4 mg, 58%) and exhibited the
following properties: Rf = 0.23 (silica gel, 6% MeOH in
Methylene chloride); [α]22D -20.0 (c 0.2, CHCl3); IR
(thin film) nmax 3448, 2919, 1725, 1684, 1455, 1378, 1284,
1149, 1061, 1020, 973, 750 cm-1; 1H NMR (500 MHz, CHCl3) d
6.99 (s, 1 H, SCH=C), 6.68 (s, 1 H, CH=CCH3), 5.64-5.61
(m, 1 H, O=COCH), 4.43 (d, J = 2.1 Hz, 1 H, OH), 4.29

(ddd, J = 7.6, 2.5, 2.5 Hz, 1 H, CHOH), 3.82 (d, J = 8.2 Hz, 1 H, CHOH), 3.35 (bs, 1 H, OH), 3.22 (q, J = 7.0 Hz, 1 H, C(O)CHCH3), 3.14 (ddd, J = 10.3, 4.1, 3.2 Hz, 1 H, CH2CHO), 2.90 (ddd, J = 10.3, 4.3, 2.3 Hz, 1 H, CH2CHO), 2.71 (s, 3 H, N=C(CH3)S), 2.54 (dd, J = 13.7, 7.6 Hz, 1 H, CH2COO), 2.51 (dd, J = 13.7, 2.5 Hz, 1 H, CH2COO), 2.21-2.19 (m, 1 H, CH2CHO), 2.18 (s, 3 H, CH=C(CH3)), 1.94 (ddd, J = 15.3, 10.3, 3.7 Hz, 1 H, CH2CHO), 1.77-1.69 (m, 2 H, CH2CHO), 1.60-1.00 (m, 5 H, CH(CH3), 2 x CH2), 1.15 (s, 3 H, C(CH3)2), 1.14 (d, J = 6.9 Hz, 3 H, CH(CH3)), 1.06 (s, 3 H, C(CH3)2), 1.02 (d, J = 7.0 Hz, 3 H, CH(CH3)); 13C NMR (150.9 MHz, CHCl3) d 221.8, 172.1, 165.1, 152.6, 134.7, 119.8, 116.8, 76.0, 74.4, 72.8, 56.4, 53.8, 53.0, 40.2, 39.1, 34.1, 32.7, 29.4, 27.8, 22.7, 20.9, 19.0, 16.1, 15.9, 15.0, 11.8; FAB HRMS (NBA) m/e 494.2587, M + H+ calcd for C26H39NO6S 494.2576.

Synthesis of Olefinic Compound 115 as illustrated in Figure 16. Phosphonium salt 79 (9.0 g, 12.93 mmol, 1.5 equiv; vida supra) was dissolved in THF (90 mL) and the solution was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF, 12.84 mL, 12.84 mmol, 1.48 equiv) was slowly added and the resulting mixture was stirred at 0 °C for 15 min. The reaction mixture was then cooled to -20 °C before ketone 78 (2.23 g, 8.62 mmol, 1.0 equiv) in THF (10 mL) was added and the reaction mixture was stirred at the same temperature for 12 h. Saturated aqueous NH4Cl solution (50 mL) was added and the mixture was extracted with ether

(200 mL). The organic phase was washed with brine (2 x
100 mL), dried (MgSO4) and concentrated to afford, after
flash column chromatography (silica gel, 2% ether in
hexanes) olefins 115 (3.8g, 73%, Z:E ca. 1:1 by 1H NMR):
Rf = 0.56 (silica gel, 20% ether in hexanes); IR (thin
film) nmax 2931, 2857, 1465, 1386, 1253, 1089, 942, 838,
776 cm-1; 1H NMR (600 MHz, CDCl3) d 6.90, 6.89 (singlets,
1 H total, SCH=C), 6.44 (s, 1 H, CH=CCH3), 5.15-5.10 (m, 1
H, C(CH3)=CH), 4.08 (m, 1 H, CHOSi), 3.42 (m, 1 H,
CH2OSi), 3.33 (dd, J = 13.3, 6.8 Hz, 0.5 H, CH2OSi), 3.32
(dd, J = 13.3, 6.7 Hz, 0.5 H, CH2OSi), 2.69 (s, 3 H,
N=C(S)CH3), 2.31-2.19 (m, 2 H, CH2CHOSi), 1.99 (s, 3 H,
CH=CCH3), 1.99-1.96 (m, 1 H, CH2C(CH3)=CH), 1.95-1.91 (m,
1 H, CH2C(CH3)=CH), 1.65 (s, 1.5 H, C(CH3)=CH), 1.58 (s,
1.5 H, C(CH3)=CH), 1.56-1.52 (m, 1 H), 1.43-1.28 (m, 3 H),
1.05-0.97 (m, 1 H), 0.88 (s, 18 H, 2 x SiC(CH3)3), 0.86
(d, J = 6.8 Hz, 1.5 H, CH3CH), 0.83 (d, J = 6.7 Hz, 1.5 H,
CH3CH), 0.04 (s, 3 H, Si(CH3)2), 0.02 (s, 3 H, Si(CH3)2),
0.01 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H, Si(CH3)2); 13C NMR
(150.9 MHz, CDCl3) d 164.2, 153.3, 142.7, 142.6, 136.9,
136.8, 121.4, 120.6, 118.6, 118.5, 114.9, 114.8, 79.0,
78.8, 68.3, 40.1, 35.8, 35.7, 35.5, 35.4, 33.2, 32.9,
32.3, 25.9, 25.8, 25.4, 25.3, 23.5, 19.2, 18.3, 18.2,
16.7, 16.2, 13.9, -4.6, -4.9, -5.3; FAB HRMS (NBA) m/e
552.3710, M + H+ calcd for C30H57NO2SSi2 552.3727.

**Synthesis of Hydroxy Olefins 116 as illustrated in
Figure 16. Desilylation of Silylether 115.** Silylether
115 (3.80 g, 6.88 mmol) was dissolved in Methylene

chloride : MeOH (1:1, 70 mL) and the solution was cooled
to 0 °C prior to addition of CSA (1.68 g, 7.23 mmol, 1.05
equiv) during a 5 min period. The resulting mixture was
stirred for 30 min at 0 °C, and then for 1 h at 25 °C.

5   Et3N (1.57 mL, 7.23 mmol, 1.05 equiv) was added, and the
solvents were removed under reduced pressure. Flash
column chromatography (silica gel, 50% ether in hexanes)
furnished pure hydroxy compound 116 (2.9 g, 97%): Rf =
0.33 (silica gel, 50% ether in hexanes); IR (thin

10 film)nmax 3370, 2929, 2857, 1463, 1382, 1252, 1185, 1072,
836, 776 cm-1; 1H NMR (600 MHz, CDCl3) (mixture of Z:E
olefins, ca 1:1) d 6.91, 6.90 (singlets, 1 H total,
SCH=C), 6.43, 6.41 (singlets, 1 H total, CH=CCH3), 5.14
(t, J = 6.9 Hz, 0.5 H, C(CH3)=CH), 5.06 (t, J = 6.8 Hz,

15 0.5 H, C(CH3)=CH), 4.08 (m, 1 H, CHOSi), 3.47 (dd, J =
10.4, 5.9 Hz, 0.5 H, CH2OH), 3.41 (dd, J = 10.6, 6.1 Hz,
0.5 H, CH2OH), 3.40-3.36 (m, 1 H, CH2OH), 2.68 (s, 3 H,
N=C(S)CH3), 2.31-2.18 (m, 2 H, CH2CHOSi), 2.05-1.99 (m, 1
H, CH2C(CH3)=CH), 1.96, 1.95 (singlets, 3 H total,

20 CH=CCH3), 1.95-1.93 (m, 1 H, CH2C(CH3)=CH), 1.65 (s, 1.5
H, C(CH3)=CH), 1.56 (s, 1.5 H, C(CH3)=CH), 1.60-1.51 (m, 1
H), 1.52-1.27 (m, 3 H), 1.10-0.96 (m, 1 H), 0.89 (d, J =
6.9 Hz, 1.5 H, CH3CH), 0.87 (s, 9 H, SiC(CH3)3), 0.85 (d,
J = 6.8 Hz, 1.5 H, CH3CH), 0.04, 0.03 (singlets, 3 H

25 total, Si(CH3)2), -0.01, -0.02 (singlets, 3 H total,
Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 164.5, 164.4,
153.0, 152.9, 142.7, 142.3, 136.7, 136.5, 121.5, 120.5,
118.8, 118.6, 114.9, 114.8, 114.7, 79.1, 78.8, 68.2,
68.1, 39.7, 35.7, 35.6, 35.4, 35.2, 33.0, 32.4, 32.1,

25.9, 25.2, 24.8, 23.4, 19.1, 18.9, 18.2, 18.1, 16.6, 16.3, 15.9, 13.9, 13.7, -4.7, -4.9; FAB HRMS (NBA) m/e 438.2875, M + H+ calcd for $C_{24}H_{43}NO_2SSi$ 438.28.

5 **Synthesis of Aldehyde 75' as illustrated in Figure 16.** Oxidation of Alcohol 116. Alcohol 116 (mixtures of Z and E geometrical isomers, 4.60 g, 10.64 mmol) was dissolved in Methylene chloride (105 mL, 0.1 M). DMSO (35 mL), Et3N (7.4 mL, 53.20 mmol, 5.0 equiv) and SO3·pyr (3.4

10 g, 21.28 mmol, 2.0 equiv) were added at 25 °C and the resulting mixture was stirred for 30 min. Saturated aqueous NH4Cl solution (50 mL) and ether (300 mL) were added, and the organic phase was separated and washed with brine (2 x 30 mL), dried (MgSO4), and concentrated under

15 reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) furnished aldehyde 75' (4.40 g, mixture of Z:E isomers, ca 1:1, 95%): Rf = 0.48 (silica gel, 50% ether in hexanes); IR (thin film) nmax 2931, 2860, 1725, 1495, 1455, 1378, 1249, 1173, 1073, 938, 832,

20 773 cm-1; 1H NMR (500 MHz, CDCl3) d 9.60, (d, J = 1.9 Hz, 0.5 H, CHO), 9.55 (d, J = 1.9 Hz, 0.5 H, CHO), 6.92, 6.91 (singlets, 1 H total, SCH=C), 6.45, 6.44 (singlets, 1 H total, CH=CCH3), 5.18-5.13 (m, 1 H, CH2CH=CCH3), 4.12-4.07 (m, 1 H, CHOSi), 2.71, 2.70 (singlets, 3 H total,

25 N=C(S)CH3), 2.36-2.20 (m, 3 H), 2.07-1.90 (m, 1 H), 1.99 (s, 3 H, CH=CCH3), 1.71-1.60 (m, 1 H), 1.66 (d, J = 1.0 Hz, 1.5 H, CH2CH=CCH3), 1.58 (d, J = 1.0 Hz, 1.5 H, CH2CH=CCH3), 1.43-1.25 (m, 4 H), 1.08 (d, J = 7.0 Hz, 1.5 H, CH3CH), 1.04 (d, J = 7.0 Hz, 1.5 H, CH3CH), 0.88 (s, 9

H, SiC(CH3)3), 0.05, 0.04 (singlets, 3 H total, Si(CH3)2),
-0.01 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d
205.2, 205.0, 164.4, 153.1, 142.3, 136.0, 135.9, 122.0,
121.2, 118.7, 118.6, 115.0, 114.9, 78.8, 78.7, 46.2, 46.1,
35.4, 35.3, 31.7, 31.6, 30.2, 30.0, 25.7, 25.1, 25.0,
23.3, 22.6, 19.1, 18.2, 16.1, 14.0, 13.9, 13.8, 13.3,
13.2, -4.8, -5.1; FAB HRMS (NBA) m/e 436.2715, M + H+
calcd for C24H41NO2SSi 436.2706.

**Synthesis of tris(silylethers) 119' and 120' as
illustrated in Figure 16.** Aldol Reaction of Keto Acid
76 with Aldehyde 75'. A solution of keto acid 76 (773 mg,
2.56 mmol, 1.2 equiv; vida supra) in THF (7.0 mL) was
reacted with aldehyde 75' (930 mg, mixture of Z:E olefins,
ca 1:1, 2.13 mmol, 1.0 equiv) according to the same
procedure as described above for the condensation of 76
and 74 (Figure 14), to afford, after similar processing,
pure carboxylic acids 119' (564 mg, mixture of Z and E
isomers, ca 1:1, 31% from 8') and 120' (545 mg, mixture of
Z and E isomers, ca 1:1, 30% from 8') as colorless oils
and recovered keto acid 76 (125 mg). 119': Rf = 0.56
(silica gel, 5% MeOH in Methylene chloride); IR (thin
film) nmax 2942, 2856, 1706, 1464, 1388, 1361, 1248, 1183,
1087, 989, 833, 774, 731 cm-1; 1H NMR (600 MHz, CDCl3) d
6.89 (s, 1 H, SCH=C), 6.50, 6.49 (singlets, 1 H total,
CH=CCH3), 5.15 (m, 1 H, (CH3)C=CHCH2), 4.39 (m, 1 H,
(CH3)2CCHOSi), 4.10-4.03 (m, 1 H, CH2CHOSi), 3.78-3.70 (m,
1 H, CH(CH3)CHOSi), 3.13 (dq, J = 7.2, 6.7 Hz, 1 H,
C(O)CH(CH3)), 2.68 (s, 3 H, N=C(CH3)S), 2.49 (dd, J =

16.4, 2.6 Hz, 0.5 H, CH2COOH), 2.44 (dd, J = 16.4, 3.1 Hz,
0.5 H, CH2COOH), 2.31-2.15 (m, 3 H, CH2COOH,
CH2C(CH3)=CHCH2), 2.05-1.85 (m, 2 H, CH2C(CH3)=CH), 1.95
(s, 1.5 H, CH=C(CH3)), 1.94 (s, 1.5 H, CH=C(CH3)), 1.64
(s, 1.5 H, CH2C(CH3)=CH), 1.55 (s, 1.5 H, CH2C(CH3)=CH),
1.45-1.25 (m, 4 H), 1.19 (s, 3 H, C(CH3)2), 1.10 (s, 3 H,
C(CH3)2), 1.21-1.09 (m, 1 H), 1.06 (d, J = 6.8 Hz, 1.5 H,
CH(CH3)), 1.05 (d, J = 6.8 Hz, 1.5 H, CH(CH3)), 0.90-0.85
(m, 30 H, CH(CH3), 3 x SiC(CH3)3), 0.10 (s, 1.5 H,
Si(CH3)2), 0.08 (s, 1.5 H, Si(CH3)2), 0.07 (s, 1.5 H,
Si(CH3)2), 0.05 (s, 1.5 H, Si(CH3)2), 0.04 (s, 3 H,
Si(CH3)2), 0.03 (s, 3 H, Si(CH3)2), 0.02 (s, 3 H,
Si(CH3)2), -0.02 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz,
CDCl3) d 218.1, 217.9, 176.7, 176.6, 164.8, 152.8, 142.9,
142.8, 136.7, 121.5, 120.5, 118.4, 118.3, 114.6, 78.9,
78.8, 77.7, 77.3, 73.5, 73.4, 53.5, 53.4, 45.3, 44.8,
40.4, 40.1, 38.9, 38.6, 35.4, 35.3, 32.5, 31.0, 30.4,
26.2, 26.0, 25.8, 25.7, 25.6, 23.5, 23.4, 19.1, 18.8,
18.7, 18.5, 18.4, 18.2, 17.8, 17.6, 17.3, 16.2, 15.8,
15.6, 13.9, 13.8, -3.6, -3.7, -3.9, -4.2, -4.3, -4.6, -
4.7, -5.0; FAB HRMS (NBA/CsI) m/e 984.4422, M + Cs+ calcd
for C45H85NO6SSi3 984.4460. 53': Rf = 0.65 (silica gel,
5% MeOH in Methylene chloride); IR (thin film) nmax 2954,
2856, 1713, 1470, 1386, 1253, 1080, 988, 836, 776 cm-1; 1H
NMR (600 MHz, CDCl3) d 6.91 (s, 1 H, SCH=C), 6.45 (s, 1
H, CH=CCH3), 5.13 (dd, J = 7.0, 6.9 Hz, 0.5 H,
(CH3)C=CHCH2), 5.09 (dd, J = 7.1, 6.9 Hz, 0.5 H,
(CH3)C=CHCH2), 4.58 (dd, J = 6.1, 3.5 Hz, 0.5 H,
(CF3)2CCHOSi), 4.56 (dd, J = 6.0, 3.5 Hz, 0.5 H,

(CH3)2CCHOSi), 4.16 (dd, J = 6.7, 6.6 Hz, 0.5 H,
CH2CHOSi), 4.06 (dd, J = 6.7, 6.0 Hz, 0.5 H, CH2CHOSi),
3.85-3.80 (m, 1 H, CH(CH3)CHOSi), 3.11 (dq, J = 7.1, 7.0
Hz, 1 H, C(O)CH(CH3)), 2.74 (s, 3 H, N=C(CH3)S), 2.43-2.10

5   (m, 4 H), 1.96-1.80 (m, 2 H), 1.92 (s, 1.5 H, CH=C(CH3)),
1.91 (s, 1.5 H, CH=C(CH3)), 1.66 (s, 1.5 H, CH2C(CH3)=CH),
1.56 (s, 1.5 H, CH2C(CH3)=CH), 1.35-1.02 (m, 14 H,
CH(CH3), 2 x CH2, C(CH3)2, C(CH3)2, CH(CH3)), 0.92-0.80
(m, 30 H, 3 x SiC(CH3)3, CH(CH3)), 0.10--0.03 (m, 18 H, 3

10   x Si(CH3)2); 13C NMR (150.9 MHz, CDC13) d   218.1, 217.9,
174.8, 174.7, 165.6, 165.5, 152.4, 143.6, 137.0, 136.8,
121.4, 121.0, 118.4, 117.9, 114.4, 78.9, 78.6, 76.4, 72.4,
72.3, 53.9, 53.8, 45.8, 45.7, 40.3, 40.2, 39.4, 38.4,
37.5, 35.6, 35.3, 35.0, 34.7, 32.2, 26.6, 26.3, 26.0,

15   25.8, 25.6, 23.8, 23.1, 22.7, 19.1, 18.7, 18.6, 18.5,
18.4, 18.2, 17.1, 16.9, 14.0, 13.8, 13.6, 13.4, -3.4, -
3.6, -4.3, -4.6, -4.7, -4.9; FAB HRMS (NBA/CsI) m/e
984.4489, M + Cs+ calcd for C45H85NO6SSi3   984.4460.

20   **Synthesis of Hydroxy Acid 73'as illustrated in
Figure 16.** Selective Desilylation of 119'. Carboxylic
acid 119' (300 mg, mixture of Z and E isomers, ca 1 : 1,
0.35 mmol) was converted to hydroxy acid 73' (194 mg,
mixture of Z and E isomers, ca 1:1, 75%) according to the

25   same procedure described above for hydroxy acid 72 (Figure
14). Compound 73': Yellow oil; Rf = 0.41 (silica gel, 5%
MeOH in Methylene chloride); IR (thin film) nmax 3260,
2923, 2852, 1707, 1463, 1381, 1249, 1187, 1085, 984, 831,
775 cm-1; 1H NMR (500 MHz, CDC13) d 6.95, 6.94 (singlets,

1 H total, SCH=C), 6.62, 6.57 (singlets, 1 H total,
CH=CCH3), 5.20-5.14 (m, 1 H, CH3C=CHCH2), 4.41 (dd, J =
6.0, 3.5 Hz, 0.5 H, (CH3)2CCHOSi), 4.37 (dd, J = 7.0, 3.0
Hz, 0.5 H, (CH3)2CCHOSi), 4.16 (dd, J = 6.6, 6.5 Hz, 1
H, CH2CHOH), 3.77 (d, J = 6.9 Hz, 1 H, CH(CH3)CHOSi),
3.17-3.09 (m, 1 H, C(O)CHCH3), 2.72, 2.71 (singlets, 3 H
total, N=C(CH3)S), 2.50 (dd, J = 16.0, 6.0 Hz, 0.5 H,
CH2COOH), 2.47 (dd, J = 16.0, 2.7 Hz, 0.5 H, CH2COOH),
2.40-2.28 (m, 3 H), 2.17-2.10 (m, 1 H), 2.00 (s, 1.5 H,
CH=C(CH3)), 1.98 (s, 1.5 H, CH=C(CH3)), 1.99-1.90 (m, 1
H), 1.70 (s, 1.5 H, CH2C(CH3)=CH), 1.62 (s, 1.5 H,
CH2C(CH3)=CH), 1.53-1.30 (m, 5 H), 1.19 (s, 3 H, C(CH3)2),
1.11 (s, 1.5 H, C(CH3)2), 1.10 (s, 1.5 H, C(CH3)2), 1.06
(d, J = 6.7 Hz, 1.5 H, CH(CH3)), 1.04 (d, J = 6.7 Hz,
1.5 H, CH(CH3)), 0.89 (s, 18 H, SiC(CH3)3), 0.86 (d, J =
7.0 Hz, 3 H, CH(CH3)), 0.09 (s, 3 H, Si(CH3)2), 0.06 (s, 6
H, Si(CH3)2), 0.05 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz,
CDCl3) d 218.0, 217.9, 176.4, 176.1, 165.0, 164.9, 152.6,
152.5, 142.1, 141.8, 139.2, 138.9, 120.3, 119.5, 118.8,
118.7, 115.2, 115.1, 77.5, 77.4, 73.4, 73.3, 53.7, 53.5,
45.1, 44.8, 40.3, 40.1, 38.9, 38.7, 34.1, 34.0, 32.5,
31.1, 30.5, 26.3, 26.2, 26.0, 23.6, 23.4, 19.2, 19.1,
18.9, 18.8, 18.5, 18.4, 18.2, 17.6, 17.2, 16.3, 15.9,
15.8, 14.5, 14.4, -3.6, -3.7, -3.8, -3.9, -4.2, -4.6; FAB
HRMS (NBA/CsI) m/e 870.3564, M + Cs+ calcd for
C39H71NO6SSi2 870.3595.

**Synthesis of Lactones 121 and 122 as illustrated in
Figure 16.** Macrolactonization of Hydroxy Acid 73'. A

solution of hydroxy acid 73' (140 mg, mixture of Z and E
isomers, ca 1:1, 0.189 mmol) in THF (2.6 mL) was treated
at 0 °C with Et3N (58 mL, 0.416 mmol, 2.2 equiv) and
2,4,6-trichlorobenzoyl chloride (29.4 mL, 0.246 mmol, 1.3
equiv). The reaction mixture was stirred at 0 °C for 1
h, and then added to a solution of 4-DMAP (233 mg, 1.896
mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and
stirred at that temperature for 10 h. The solvents were
removed in vacuo, and the crude product obtained was
suspended in 40% ether in hexanes and filtered through
silica gel. Concentration, followed by preparative thin
layer chromatography (silica gel, 5% MeOH in Methylene
chloride), gave pure lactones 121 (50 mg, 37%) and 122 (54
mg, 40%) as colorless oils. 121: Rf = 0.40 (silica gel, 1%
MeOH in Methylene chloride); [a]22D -11.8 (c 0.8, CHCl3);
IR (thin film) nmax 2931, 2848, 1737, 1690, 1461, 1378,
1249, 1184, 1158, 1097, 1020, 984, 835, 775 cm-1; 1H NMR
(600 MHz, CDCl3) d 6.95 (s, 1 H, SCH=C), 6.56 (s, 1 H,
CH=CCH3), 5.16 (dd, J = 8.4, 7.5 Hz, 1 H, CH3C=CHCH2),
4.96 (d, J = 10.1 Hz, 1 H, CH2COOCH), 4.02 (d, J = 9.9
Hz, 1 H, CHOSi), 3.88 (d, J = 8.9 Hz, 1 H, CHOSi), 3.02
(dq, J = 6.9, 6.7 Hz, 1 H, C(O)CHCH3), 2.79 (d, J = 15.6
Hz, 1 H, CH2COOCH), 2.70 (s, 3 H, N=C(CH3)S), 2.70-2.65
(m, 2 H), 2.48-2.40 (m, 1 H), 2.10 (s, 3 H, CH=C(CH3)),
2.10-2.04 (m, 2 H), 1.75-1.69 (m, 2 H), 1.67 (s, 3 H,
CH2C(CH3)=CH), 1.66-1.45 (m, 3 H), 1.18 (s, 3 H, C(CH3)2),
1.13 (s, 3 H, C(CH3)2), 1.09 (d, J = 6.8 Hz, 3 H,
CH(CH3)), 0.97 (d, J = 6.8 Hz, 3 H, CH(CH3)), 0.94 (s, 9
H, SiC(CH3)3), 0.84 (s, 9 H, SiC(CH3)3), 0.10 (s, 3 H,

Si(CH3)2), 0.09 (s, 3 H, Si(CH3)2), 0.07 (s, 3 H, Si(CH3)2), -0.12 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDC13) d 215.1, 171.2, 164.6, 152.5, 140.6, 138.8, 119.3, 119.1, 115.9, 79.9, 76.3, 53.4, 39.1, 32.4, 31.9, 31.4, 29.7, 27.4, 26.4, 26.1, 26.0, 24.5, 24.3, 23.1, 19.2, 18.7, 18.6, 17.8, 15.3, -3.3, -3.7, -5.7; FAB HRMS (NBA) m/e 720.4534, M + H+ calcd for C39H69NO5SSi2 720.4513.

122: Rf = 0.50 (silica gel, 1% MeOH in Methylene chloride); [a]22D -22.7 (c 0.6, CHC13); IR (thin film) nmax 2931, 2860, 1731, 1696, 1461, 1378, 1249, 1179, 1079, 985, 832, 773 cm-1; 1H NMR (600 MHz, CDC13) d 6.92 (s, 1 H, SCH=C), 6.53 (s, 1 H, CH=CCH3), 5.27 (dd, J = 8.0, 2.7 Hz, 1 H, CH2COOCH), 5.16 (dd, J = 6.9, 6.6 Hz, 1 H, CH3C=CHCH2), 4.47 (t, J = 5.1 Hz, 1 H, CHOSi), 3.89 (dd, J = 4.5, 1.0 Hz, 1 H, CHOSi), 3.05 (dq, J = 6.7, 6.2 Hz, 1 H, C(O)CHCH3), 2.70 (s, 3 H, N=C(CH3)S), 2.60 (dd, J = 15.8, 5.8 Hz, 1 H, CH2COOCH), 2.55 (m, 1 H, CH3C=CHCH2), 2.51-2.47 (m, 2 H, CH2COOCH, CH3C=CHCH2), 2.13 (s, 3 H, CH=C(CH3)), 2.10-2.05 (m, 1 H, CH2C(CH3)=CH), 1.91 (m, 1 H, CH2C(CH3)=CH), 1.68-1.45 (m, 4 H), 1.57 (s, 3 H, CH2C(CH3)=CH), 1.27-1.23 (m, 1 H), 1.17 (s, 3 H, C(CH3)2), 1.04 (d, J = 6.8 Hz, 3 H, CH(CH3)), 1.07 (s, 3 H, C(CH3)2), 0.93 (d, J = 6.9 Hz, 3 H, CH(CH3)), 0.88 (s, 9 H, SiC(CH3)3), 0.86 (s, 9 H, SiC(CH3)3), 0.07 (s, 6 H, Si(CH3)2), 0.06 (s, 3 H, Si(CH3)2), 0.05 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDC13) d 217.2, 171.3, 165.5, 153.6, 139.0, 138.3, 120.9, 120.2, 117.0, 80.1, 77.2, 73.9, 54.8, 44.9, 42.7, 41.1, 40.2, 32.8, 26.9, 26.8, 25.6, 23.5, 21.1, 20.1, 19.2, 19.1, 17.7, 16.8,

16.6, 16.3, -2.7, -3.1, -3.4, -3.6; FAB HRMS (NBA) m/e
720.4533, M + H+ calcd for C39H69NO5SSi2 720.4513.

Synthesis of Dihydroxy lactone 71 as illustrated in
Figure 16. Dihydroxy lactone 71 was prepared from
bis(silylether) lactone 121 (13.3 mg, 0.018 mmol) by
treatment with CF3COOH according to the same procedure
described above for the preparation of 70 (figure 14), to
obtain pure lactone 71 (8.4 mg, 91%) as a colorless oil.
71: Rf = 0.21 (silica gel, 4% MeOH in Methylene chloride);
[a]22D -91.5 (c 0.3, CHCl3); IR (thin film) nmax 3460,
2954, 2919, 1725, 1684, 1455, 1379, 1290, 1249, 1184,
1143, 1043, 1008, 973, 750 cm-1; 1H NMR (600 MHz, CDCl3) d
6.94 (s, 1 H, SCH=C), 6.57 (s, 1 H, CH=CCH3), 5.20 (d, J =
9.7 Hz, 1 H, CH2COOCH), 5.13 (dd, J = 9.6, 4.6 Hz, 1 H,
CH3C=CHCH2), 4.28 (d, J = 9.7 Hz, 1 H, (CH3)2CCHOH), 3.71
(s, 1 H, CHOH), 3.47 (bs, 1 H, OH), 3.15 (q, J = 6.8 Hz,
1 H, C(O)CHCH3), 3.04 (bs, 1 H, OH), 2.68 (s, 3 H,
N=C(CH3)S), 2.62 (ddd, J = 15.0, 10.2, 10.1 Hz, 1 H,
CH2CH=CCH3), 2.45 (dd, J = 14.7, 11.1 Hz, 1 H, CH2COOCH),
2.38-2.24 (m, 1 H), 2.28 (dd, J = 14.8, 2.2 Hz, CH2COOCH),
2.22 (d, J = 14.9 Hz, 1 H, CH2C(CH3)=CHCH2), 2.06 (s, 3 H,
CH=CCH3), 1.90-1.84 (m, 1 H), 1.76-1.69 (m, 1 H), 1.65 (s,
3 H, CH2C(CH3)=CH), 1.33 (s, 3 H, C(CH3)2), 1.32-1.22 (m,
4 H), 1.19 (d, J = 6.8 Hz, 3 H, CH(CH3)), 1.06 (s, 3 H,
C(CH3)2), 1.00 (d, J = 7.0 Hz, 3 H, CH(CH3)); 13C NMR
(150.9 MHz, CDCl3) d 220.4, 170.2, 164.9, 151.8, 139.1,
138.3, 120.8, 119.1, 115.5, 78.9, 74.1, 72.3, 53.6, 41.7,
39.7, 32.6, 31.8, 31.7, 25.4, 23.0, 19.1, 18.1, 16.0,

15.8, 13.5; FAB HRMS (NBA) m/e 492.2795, M + H+ calcd for C27H41NO5S 492.2784.

Synthesis of Dihydroxy Lactone 123 as illustrated in Figure 16. Dihydroxy lactone 123 was prepared from bis(silylether) lactone 122 (40.0 mg, 0.055 mmol) by treatment with CF3COOH according to the same procedure described above for the preparation of 70 (Figure 14). Obtained pure 123 (24.3 mg, 89%): Rf = 0.19 (silica gel, 4% MeOH in Methylene chloride); [a]22D -61.0 (c 0.2, CHCl3); IR (thin film) nmax 3418, 2932, 1731, 1691, 1466, 1381, 1252, 1159, 1067, 1044, 1012, 978, 755 cm-1; 1H NMR (600 MHz, CDCl3) d 6.99 (s, 1 H, SCH=C), 6.54 (s, 1 H, CH=CCH3), 5.38 (dd, J = 6.7, 3.8 Hz, 1 H, CH2COOCH), 5.08 (t, J = 6.9 Hz, 1 H, CH3C=CHCH2), 4.32 (dd, J = 10.0, 2.4 Hz, 1 H, (CH3)2CCHOH), 3.65 (t, J = 3.4 Hz, 1 H, CHOH), 3.25 (dq, J = 6.7, 3.9 Hz, 1 H, C(O)CHCH3), 2.68 (s, 3 H, N=C(CH3)S), 2.55-2.43 (m, 3 H, CH2COOCH, C(CH3)=CHCH2), 2.40 (dd, J = 15.3, 2.5 Hz, 1 H, CH2COOCH), 2.17-2.10 (m, 1 H, CH2C(CH3)=CH), 2.05 (s, 3 H, CH=CCH3), 1.95 (ddd, J = 13.4, 10.0, 3.3 Hz, 1 H, CH2C(CH3)=CH), 1.70-1.57 (m, 3 H), 1.57 (s, 3 H, CH2C(CH3)=CH), 1.50-1.35 (m, 2 H), 1.33 (s, 3 H, C(CH3)2), 1.15 (d, J = 6.8 Hz, 3 H, CH(CH3)), 1.03 (s, 3 H, C(CH3)2), 0.97 (d, J = 7.0 Hz, 3 H, CH(CH3)); 13C NMR (150.9 MHz, CDCl3) d 220.7, 170.7, 165.3, 152.3, 138.5, 137.4, 119.6, 119.4, 115.7, 77.7, 76.2, 71.6, 52.7, 42.7, 39.4, 39.0, 37.3, 30.7, 24.5, 20.5, 19.7, 18.7, 15.9, 15.8, 15.5, 14.3; FAB HRMS (NBA) m/e 492.2772, M + H+ calcd for C27H41NO5S 492.2784.

Synthesis of Epothilone B (2) and its α-epoxide epimer 126 as illustrated in Figure 16. Epoxidation of Lactone 71 . Procedure A: To a solution of lactone 71 (3.0 mg, 6.1 mmol) in benzene (0.2 mL) at -10 °C was added meta-chloroperbenzoic acid (2.9 mg, 50-60% purity, 8.4-10.1 mmol, 1.4-1.6 equiv) and the reaction mixture was stirred at that temperature for 2 h at which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous NaHCO3 solution (2 mL), and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic layer was dried (MgSO4), filtered and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) provided a mixture of epothilone B (2) and its α-epoxy diastereoisomer 124 (2.0 mg, 66%, ca 5:1 ratio by 1H NMR), which was separated to its components by a second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnishing pure epothilone B (2) (1.6 mg, 52%) as a white solid. Procedure B: To a solution of lactone 71 (5.0 mg, 10.2 mmol) in Methylene chloride (0.5 mL) at -50 °C was added dropwise a solution of dimethyldioxirane in acetone untill the starting material disappeared (TLC). The resulting solution was concentrated, and the crude product was subjected to preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) to give epothilone B (2) and its a-epoxy diastereoisomer 124 in ca 5:1 ratio (3.9 mg, 75%).

Pure epothilone B (2) was obtained (3.1 mg, 60%) by
preparative thin layer chromatography as described above.
Procedure C: Lactone 71 (3.0 mg, 6.1 mmol) was epoxidised
with methyl(trifluoromethyl)dioxirane according to the
procedure described above for the epoxidation of 70
(figure 14), to yield a mixture of 2 and its α-epoxy
diastereoisomer 124 in ca 5:1 ratio by 1H NMR (2.6 mg, 85%
yield). The major diastereoisomer, epothilone B (2) was
isolated as described above (2.1 mg, 69%). 2: Colorless
crystals; mp 93 °C (crystallized in Methylene
chloride/petroleum ether); Rf = 0.24 (silica gel, 4% MeOH
in Methylene chloride); [a]22D -34.3 (c 0.2, MeOH); IR
(thin film) nmax 3436, 2954, 2931, 1731, 1684, 1455, 1373,
1290, 1249, 1184, 1143, 1043, 1049, 973, 750 cm-1; 1H NMR
(600 MHz, CDC13) d 6.97 (s, 1 H, SCH=C), 6.59 (s, 1 H,
CH=CCH3), 5.41 (dd, J = 7.8, 2.8 Hz, 1 H, CH2COOCH), 4.22
(bs, 2 H, (CH3)2CCHOH, OH), 3.77 (dd, J = 4.3, 4.2 Hz, 1
H, CHOH), 3.30 (dq, J = 6.8, 4.1 Hz, 1 H, C(O)CHCH3),
2.80 (dd, J = 7.6, 4.7 Hz, 1 H, CHOCCH3), 2.70 (s, 3 H,
N=C(CH3)S), 2.64 (bs, 1 H, OH), 2.54 (dd, J = 14.0, 10.2
Hz, 1 H, CH2COOCH), 2.36 (d, J = 14.0, 2.9 Hz, 1 H,
CH2COOCH), 2.12 (dd, J = 4.7, 2.8 Hz, 1 H,
(CH3)COCHCH2CHO), 2.08 (s, 3 H, CH=CCH3), 1.91 (ddd, J =
15.4, 7.8, 7.6 Hz, 1 H, (CH3)COCHCH2CHO), 1.77-1.68 (m, 3
H), 1.53-1.46 (m, 2 H), 1.43-1.37 (m, 2 H), 1.36 (s, 3 H,
C(CH3)OCHCH2), 1.27 (s, 3 H, C(CH3)2), 1.16 (d, J = 6.9
Hz, 3 H, CH(CH3)), 1.08 (s, 3 H, C(CH3)2), 1.00 (d, J =
7.0 Hz, 3 H, CH(CH3)); 1H NMR (600 MHz, DMSO-d6) d 7.34
(s, 1 H, SCH=C), 6.49 (s, 1 H, CH=CCH3), 5.27 (dd, J =

9.0, 2.0 Hz, 1 H, CH2COOCH), 5.07 (d, J = 6.9 Hz, 1 H,
OH), 4.45 (bs, 1 H, OH), 4.08 (m, 1 H, (CH3)2CCHOH), 3.47
(d, J = 7.4 Hz, 1 H, CHOH), 3.10 (dq, J = 6.8, 6.5 Hz,
1 H, C(O)CHCH3), 2.81 (dd, J = 9.5, 3.3 Hz, 1 H, CHOCCH3),

5   2.64 (s, 3 H, N=C(CH3)S), 2.40-2.30 (m, 2 H, CH2COOCH),
2.08 (s, 3 H, CH=CCH3), 2.05 (ddd, J = 15.0, 2.6, 1.0 Hz,
1 H, (CH3)COCHCH2CHO), 1.83 (ddd, J = 15.0, 9.3, 9.1 Hz, 1
H, (CH3)COCHCH2CHO), 1.61 (m, 1 H), 1.45-1.35 (m, 3 H),
1.35-1.25 (m, 3 H), 1.17 (s, 6 H, C(CH3)OCHCH2, C(CH3)2),

10   1.05 (d, J = 6.6 Hz, 3 H, CH(CH3)), 0.87 (d, J = 7.0 Hz,
3 H, CH(CH3)), 0.86 (s, 3 H, C(CH3)2); 13C NMR (150.9 MHz,
DMSO-d6) d 218.1, 170.7, 164.8, 152.5, 137.6, 119.5,
118.0, 76.7, 75.7, 70.7, 61.6, 61.1, 53.3, 44.9, 35.6,
33.0, 32.1, 29.6, 23.0, 22.4, 22.0, 19.7, 18.8, 18.4,

15   16.4, 14.1; FAB HRMS (NBA/CsI) m/e 640.1725, M + Cs+
calcd for C27H41NO6S 640.1709. A natural sample of
epothilone B (2) exhibited identical properties to those
reported above.

20   **Synthesis of Epothilone 125 and 126 as illustrated
in Figure 16. Epoxidation of Lactone 123. Procedure A:**
Compound 123 (5.0 mg, 10.2 mmol) was epoxidised with mCPBA
according to procedure A described above for 2 to yield a
mixture of 12S-epi-epothilone B (125) and its α-epoxy-

25   diastereoisomer 126 (3.7 mg, 73% total yield, ca 4:1 by 1H
NMR). Purification by preparative thin layer
chromatography (silica gel, 5% MeOH in Methylene chloride)
gave pure 12S-epothilone 126 (2.5 mg, 49%) as a white
solid. Procedure B: The epoxidation of 123 (3.0 mg, 6.1

mmol) according to the procedure described above for 1 led to epothilones 126 and its α-epoxy diastereoisomer 126 (2.6 mg, 86% total yield, ca 1:1 ratio by 1H NMR). Preparative thin layer chromatography (silica gel, 5% MeOH in Methylene chloride) furnished pure epothilone 125 (1.3 mg, 43%) and its α-epoxy diastereoisomer 126 (1.3 mg, 43%). 125: Rf = 0.55 (silica gel, 5% MeOH in Methylene chloride); [α]22D -34.5 (c 0.1, CHCl3); IR (thin film) nmax 3440, 2929, 1731, 1693, 1467, 1384, 1294, 1257, 1151, 1050, 977, 755 cm-1; 1H NMR (600 MHz, CDCl3) d 6.97 (s, 1 H, SCH=C), 6.60 (s, 1 H, CH=CCH3), 5.50 (dd, J = 8.0, 4.0 Hz, 1 H, CH2COOCH), 4.25 (dd, J = 10.1, 3.2 Hz, 1 H, (CH3)2CCHOH), 3.80 (bs, 1 H, OH), 3.75 (dd, J = 5.5, 3.6 Hz, 1 H, CHOH), 3.31 (dq, J = 6.7, 6.3 Hz, 1 H, C(O)CHCH3), 2.88 (dd, J = 6.3, 4.5 Hz, 1 H, CHOCCH3), 2.69 (s, 3 H, N=C(CH3)S), 2.59 (bs, 1 H, OH), 2.55 (dd, J = 13.5, 10.4 Hz, 1 H, CH2COOCH), 2.45 (dd, J = 13.5, 3.7 Hz, 1 H, CH2COOCH), 2.08 (s, 3 H, CH=CCH3), 2.05-1.97 (m, 3 H), 1.95-1.90 (m, 1 H, (CH3)COCHCH2CHO), 1.75-1.70 (m, 2 H), 1.51-1.45 (m, 3 H), 1.37 (s, 3 H, C(CH3)OCHCH2), 1.27 (s, 3 H, C(CH3)2), 1.14 (d, J = 6.9 Hz, 3 H, CH(CH3)), 1.04 (s, 3 H, C(CH3)2), 0.95 (d, J = 6.9 Hz, 3 H, CH(CH3)); 13C NMR (150.9 MHz, CDCl3) d 219.6, 170.7, 164.9, 152.1, 136.6, 119.8, 116.4, 77.6, 75.9, 73.3, 61.3, 59.9, 52.9, 44.2, 38.8, 37.2, 36.4, 32.9, 31.3, 21.9, 21.3, 19.8, 19.4, 17.9, 17.4, 14.8; FAB HRMS (NBA/CsI) m/e 640.1686, M + Cs+ calcd for C27H41NO6S 640.1709.

Synthesis of α,β-Unsaturated Ester 127 as
illustrated in Figure 17. A mixture of aldehyde 82
(5.17 g, 15.9 mmol) and stabilized ylide 83 (8.92 g, 24.0
mmol, 1.5 equiv, prepared from 4-bromo-1-butene by: (i)
phosphonium salt formation; (ii) anion formation with
NaHMDS; and (iii) quenching with MeOC(O)Cl) as described
in Murray, R. W.; Jeyaraman, R. J. Org. Chem. 1985, 50,
2847-2853) in benzene (300 mL, 0.05 M) was heated at
reflux for 3 h. After cooling to 25 °C, the solvent was
removed under reduced pressure and the residue was
subjected to flash column chromatography (silica gel, 30%
ether in hexanes) to afford α,β-unsaturated ester 127
(7.15 g, 95%): Rf = 0.65 (silica gel, 40% ether in
hexanes); [α]22D +10.4 (c 1.4, CHCl3); IR (thin film)
nmax 2939, 2856, 1715, 1644, 1504, 1464, 1437, 1365, 1284,
1252, 1209, 1076, 955, 836, 776 cm-1; 1H NMR (500 MHz,
CDCl3) d 6.91 (s, 1 H, SCH=C), 6.87 (d, J = 7.4 Hz, 1 H,
CH=CCOOCH3), 6.47 (s, 1 H, CH=CCH3), 5.83-5.71 (m, 1 H,
CH=CH2), 5.01-4.92 (m, 2 H, CH=CH2), 4.19 (dd, J = 7.7,
4.9 Hz, 1 H, CHOSi), 3.69 (s, 3 H, COOCH3), 3.05 (d, J =
6.0 Hz, 2 H, CH2CH=CH2), 2.67 (s, 3 H, N=C(S)CH3), 2.46
(ddd, J = 15.1, 7.7, 7.4 Hz, 1 H, CH2CHOSi), 2.39 (ddd,
J = 15.0, 7.5, 5.0 Hz, 1 H, CH2CHOSi), 1.99 (s, 3 H,
CH=CCH3), 0.86 (s, 9 H, SiC(CH3)3), 0.03 (s, 3 H,
Si(CH3)2), -0.02 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz,
CDCl3) d 167.8, 164.4, 152.8, 141.5, 140.6, 135.3, 130.7,
119.1, 115.5, 115.1, 77.6, 51.7, 36.1, 30.9, 25.7, 19.2,
18.1, 13.9, -4.7, -5.1; FAB HRMS (NBA/CsI) m/e 554.1168, M

+ Cs+ calcd for C22H35NO3SSi 554.1161.

**Synthesis of Allylic Alcohol 128 as illustrated in
Figure 17.** Methyl ester 127 (6.1 g, 14.4 mmol) was
dissolved in THF (80 mL) and cooled to -78 °C. DIBAL
(44.0 mL, 1 M solution in Methylene chloride, 44.0 mmol,
3.0 equiv) was added dropwise at -78 oC, and the reaction
mixture was stirred for 3 h. The reaction mixture was
quenched with MeOH (1.0 mL) at -78 °C, and then ether (100
mL) was added, followed by saturated aqueous sodium-
potassium tartrate solution (10 mL). The resulting mixture
was allowed to warm up to room temperature, where it was
stirred for 3 h. The organic layer was separated and the
aqueous phase was extracted with ether (2 x 50 mL). The
combined organic phase was dried (MgSO4), filtered and
concentrated under reduced pressure. Flash column
chromatography (silica gel, 40 to 80% ether in hexanes)
furnished alcohol 128 (5.58 g, 98%): Rf = 0.18 (silica
gel, 40% ether in hexanes); [a]22D +6.6 (c 1.1, CHCl3); IR
(thin film) nmax 3380, 2928, 2855, 1637, 1505, 1464, 1386,
1253, 1185, 1074, 836, 776 cm-1; 1H NMR (600 MHz, CDCl3) d
6.88 (s, 1 H, SCH=C), 6.41 (s, 1 H, CH=CCH3), 5.77-5.69
(m, 1 H, CH=CH2), 5.48 (dd, J = 7.3, 7.2 Hz, 1 H,
CH=CCH2OH), 5.00 (dd, J = 15.5, 3.3 Hz, 1 H, CH=CH2), 4.93
(dd, J = 10.0, 3.3 Hz, 1 H, CH=CH2), 4.12 (dd, J = 6.5,
6.4 Hz, 1 H, CHOSi), 3.97 (s, 2 H, CH2OH), 2.86-2.76 (m, 2
H, CH2CH=CH2), 2.65 (s, 3 H, N=C(S)CH3), 2.53 (bs, 1 H,
OH), 2.36-2.24 (m, 2 H, CH2CHOSi), 1.94 (s, 3 H, CH=CCH3),
0.86 (s, 9 H, SiC(CH3)3), 0.02 (s, 3 H, Si(CH3)2), -0.02

(s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDC13) d 164.5, 152.8, 142.0, 138.1, 123.7, 118.7, 115.2, 114.9, 78.3, 66.6, 34.7, 32.4, 25.7, 19.0, 18.1, 13.7, -4.8, -5.0; FAB HRMS (NBA) m/e 394.2232, M + H+ calcd for C21H35NO2SSi 394.2236.

Synthesis of Compound 129 as illustrated in Figure 17. Chlorination of Alcohol 128. Alcohol 128 (3.00 g, 7.60 mmol) was dissolved in CC14 (75 mL, 0.1 M) and Ph3P (4.00 g, 15.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10% ether in hexanes) furnished pure 129 (2.6 g, 83%): Rf = 0.50 (silica gel, 15% ether in hexanes); [a]22D +13.7 (c 1.0, CHC13); IR (thin film) nmax 2953, 2928, 2855, 1637, 1504, 1470, 1439, 1387, 1254, 1182, 1075, 953, 917, 836, 776 cm-1; 1H NMR (600 MHz, CDC13) d 6.93 (s, 1 H, SCH=C), 6.47 (s, 1 H, CH=CCH3), 5.77-5.69 (m, 1 H, CH=CH2), 5.66 (dd, J = 7.5, 7.2 Hz, 1 H, CH2CH=CCH2Cl), 5.07 (dd, J = 17.1, 1.6 Hz, 1 H, CH=CH2), 5.02 (dd, J = 10.1, 1.4 Hz, 1 H, CH=CH2), 4.14 (dd, J = 7.2, 5.5 Hz, 1 H, CHOSi), 4.02 (s, 2 H, CH2Cl), 2.99-2.89 (m, 2 H, CH2CH=CH2), 2.71 (s, 3 H, N=C(S)CH3), 2.52-2.27 (m, 2 H, CH2CHOSi), 1.99 (s, 3 H, CH=CCH3), 0.88 (s, 9 H, SiC(CH3)3), 0.05 (s, 3 H, Si(CH3)2), 0.00 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDC13) d 164.3, 152.9, 141.8, 134.9, 134.7, 128.9, 119.0, 116.2, 115.2, 78.1, 49.9, 35.3, 32.3, 25.8, 19.2, 18.2, 13.9, -4.7, -5.0; FAB HRMS (NBA) m/e 412.1884, M + H+

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calcd for C21H34ClNOSSi 412.1897.

Synthesis of compound 130 as illustrated in Figure 17. Reduction of 129. Compound 129 (2.60 g, 6.30 mmol) was dissolved in THF (60 mL, 0.1 M) and cooled to 0 °C. LiEt3BH (12.6 ml, 1.0 M solution in THF, 12.6 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. Aqueous NaOH (1.0 mL, 3.0 N) solution was added followed by addition of Et20 (150 mL). The organic phase was washed with brine (2 x 20 mL), dried (MgSO4) and concentrated. Flash column chromatography (silica gel, 20% ether in hexanes) furnished pure 130 (2.38 g, 99%): Rf = 0.60 (silica gel, 15% ether in hexanes); [α]22D +17.1 (c 0.7, CHCl3); IR (thin film) nmax 2928, 2856, 1637, 1505, 1464, 1253, 1181, 1075, 946, 836, 776 cm-1; 1H NMR (600 MHz, CDCl3) d 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH3), 5.77-5.68 (m, 1 H, CH=CH2), 5.22 (dd, J = 7.3, 7.0 Hz, 1 H, CH2CH=CCH3), 5.01 (dd, J = 17.1, 3.2 Hz, 1 H, CH=CH2), 4.96 (dd, J = 10.1, 3.3 Hz, 1 H, CH=CH2), 4.09 (dd, J = 7.2, 5.9 Hz, 1 H, CHOSi), 2.80 (dd, J = 14.5, 6.5 Hz, 1 H, CH2CH=CH2), 2.73-2.68 (m, 1 H, CH2CH=CH2), 2.70 (s, 3 H, N=C(S)CH3), 2.32-2.19 (m, 2 H, CH2CHOSi), 1.99 (s, 3 H, CH=CCH3), 1.66 (s, 3 H, CH2CH=CCH3), 0.88 (s, 9 H, SiC(CH3)3), 0.04 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H, Si(CH3)2); 13C NMR (150.9 MHz, CDCl3) d 164.3, 153.2, 142.5, 136.0, 134.4, 122.5, 118.7, 115.1, 114.9, 78.9, 36.6, 35.3, 25.8, 23.5, 19.2, 18.2, 13.9, -4.8, -5.0; FAB HRMS (NBA) m/e 378.2279, M + H+ calcd for C21H35NOSSi 378.2287.

Synthesis of Primary Alcohol 131 as illustrated in Figure 17. Selective Hydroboration of Olefinic Compound 130. Compound 130 (1.1 g, 2.91 mmol) was dissolved in THF (3.0 mL, 1.0 M) and the solution was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H2O2 (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after which time the reaction mixture was diluted with ether (30 mL). The organic solution was separated and the aqueous phase was extracted with ether (2 x 15 mL). The combined organic layer was washed with brine (2 x 5 mL), dried (Na2SO4) and concentrated in vacuo. Flash column chromatography (silica gel, 50 to 80% ether in hexanes) furnished primary alcohol 131 (1.0 g, 91%): Rf = 0.17 (silica gel, 50% ether in hexanes); [α]22D +3.6 (c 0.2, CHC13); IR (thin film) nmax 3381, 2953, 2929, 2856, 1723, 1660, 1469, 1444, 1376, 1253, 1185, 1073, 941, 837, 776 cm-1; 1H NMR (600 MHz, CDC13) d 6.91 (s, 1 H, SCH=C), 6.44 (s, 1 H, CH=CCH3), 5.17 (dd, J = 7.0, 6.9 Hz, 1 H, CH2CH=CCH3), 4.11 (dd, J = 7.1, 5.7 Hz, 1 H, CHOSi), 3.59 (dd, J = 6.5, 6.4 Hz, 2 H, CH2OH), 2.70 (s, 3 H, N=C(S)CH3), 2.35-2.28 (m, 1 H, CH2CHOSi), 2.27-2.20 (m, 1 H, CH2CHOSi), 2.10 (dd, J = 7.6, 7.5 Hz, 2 H CH2CH2CH2OH), 1.98 (s, 3 H, CH=CCH3), 1.67 (s, 3 H, CH2CH=CCH3), 1.67-1.58 (m, 2 H, CH2CH2OH), 0.88 (s, 9 H, SiC(CH3)3), 0.04 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H, Si(CH3)2); 13C NMR

(150.9 MHz, CDC13) d 164.5, 153.0, 142.7, 136.2, 122.2, 118.5, 115.0, 78.9, 62.4, 35.4, 30.7, 28.0, 25.8, 23.3, 19.2, 18.3, 14.0, -4.7, -5.0; FAB HRMS (NBA) m/e 396.2382, M + H+ calcd for C21H37NO2SSi 396.2393.

Synthesis of Iodide 81 as illustrated in Figure 17.
Iodide 81 (1.18 g, 92%) was prepared from alcohol 131 (1.0 g, 2.53 mmol) according to the procedure described above for 94 (Figure 12). 81: Colorless oil; Rf = 0.65 (silica gel, 20 % ether in hexanes); [a]22D +7.5 (c 0.8, CHC13); IR (thin film) nmax 2955, 2930, 2855, 1504, 1462, 1444, 1376, 1360, 1253, 1183, 1074, 942, 837, 776 cm-1; 1H NMR (500 MHz, CDC13) d 6.91 (s, 1 H, SCH=C), 6.46 (s, 1 H, CH=CCH3), 5.20 (dd, J = 7.3, 7.1 Hz, 1 H, CH2CH=CCH3), 4.09 (dd, J = 7.4, 5.5 Hz, 1 H, CHOSi), 3.14 (dd, J = 7.1, 7.0 Hz, 2 H, CH2I), 2.69 (s, 3 H, N=C(S)CH3), 2.34-2.27 (m, 1 H, CH2CHOSi), 2.26-2.19 (m, 1 H, CH2CHOSi), 2.17-2.03 (m, 2 H), 2.00 (s, 3 H, CH=CCH3), 1.93-1.86 (m, 2 H), 1.67 (s, 3 H, CH2CH=CCH3) 0.88 (s, 9 H, SiC(CH3)3), 0.04 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDC13) d 164.2, 153.1, 142.3, 134.6, 123.1, 118.6, 115.0, 78.8, 35.4, 32.6, 31.9, 25.8, 23.4, 19.2, 18.2, 14.0, 6.5, -4.7, -5.0; FAB HRMS (NBA) m/e 506.1422, M + H+ calcd for C21H36INOSSi 506.1410.

Synthesis of Hydrazone 132 as illustrated in Figure 17. Alkylation of SAMP Hydrazone 80 with Iodide 81. SAMP hydrazone 80 (337 mg, 0.2 mmol, 2.0 equiv; Aldrich) in THF (2.5 mL), was added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 mL, 0.20

mmol, 2.0 equiv) was added to n-BuLi (1.39 mL, 1.42 M
solution in hexanes, 0.20 mmol. 2.0 equiv) in 2.5 mL of
THF at 0 °C] at 0°C. After stirring at that temperature
for 8 h, the resulting yellow solution was cooled to -100
°C, and a solution of iodide 81 (0.5 g, 0.99 mmol, 1.0
equiv) in THF (3 mL) was added dropwise over a period of 5
min. The mixture was allowed to warm to -20 °C over 10 h,
and then poured into saturated aqueous NH4Cl solution (5
mL) and extracted with ether (3 x 25 mL). The combined
organic extracts were dried (MgSO4), filtered and
evaporated. Purification by flash column chromatography
on silica gel (20 to 40% ether in hexanes) provided
hydrazone 132 (380 mg, 70%, de > 98% by 1H NMR) as a
yellow oil: Rf = 0.17 (silica gel, 20% ether in hexanes);
[a]22D -27.8 (c 2.6, CHCl3); IR (thin film) nmax 2931,
2861, 1724, 1653, 1599, 1499, 1451, 1374, 1249, 1178,
1077, 940, 834, 774, 727, 673 cm-1; 1H NMR (500 MHz,
CDCl3) d 6.91 (s, 1 H, SCH=C), 6.48 (d, J = 6.6 Hz, 1 H,
CNH), 6.44 (s, 1 H, CH=CCH3), 5.12 (dd, J = 7.1, 6.9 Hz, 1
H, CH2CH=CCH3), 4.07 (dd, J = 6.8, 6.2 Hz, 1 H, CHOSi),
3.55 (dd, J = 9.1, 3.7 Hz, 1 H, CH2OCH3), 3.41 (dd, J =
9.1, 6.9 Hz, 1 H, CH2OCH3), 3.36 (s, 3 H, CH2OCH3), 3.35-
3.32 (m, 2 H, CH2N), 2.70 (s, 3 H, N=C(S)CH3), 2.69-2.62
(m, 1 H), 2.31-2.17 (m, 3 H), 2.04-1.84 (m, 5 H), 1.99 (s,
3 H, CH=CCH3), 1.79-1.72 (m, 1 H), 1.64 (s, 3 H,
CH2CH=CCH3) 1.41-1.22 (m, 4 H), 1.01 (d, J = 6.9 Hz,
CHCH3), 0.88 (s, 9 H, SiC(CH3)3), 0.04 (s, 3 H, Si(CH3)2),
-0.01 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d
164.2, 153.1, 144.3, 142.4, 136.6, 121.5, 118.5, 114.8,

78.9, 74.7, 63.4, 59.1, 50.4, 37.0, 35.3, 35.2, 31.8,
26.4, 25.7, 25.4, 23.3, 22.0, 19.1, 18.9, 18.1, 13.8, -
4.8, -5.0; FAB HRMS (NBA) m/e 548.3728, M + H+ calcd for
$C_{30}H_{53}N_3O_2SSi$ 548.3706.

**Synthesis of Nitrile 66 as illustrated in Figure
17.** Monoperoxyphthalic acid magnesium salt (MMPP•6H2O,
233 mg, 0.38 mmol, 2.5 equiv; Aldrich) was suspended in a
rapidly stirred mixture of MeOH and pH 7 phosphate buffer
(1:1, 3.0 mL) at 0 °C. Hydrazone **132** (83 mg, 0.15 mmol,
1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the
mixture was stirred at 0 °C until the reaction was
complete by TLC (ca 1 h). The resulting suspension was
placed in a separating funnel along with ether (15 mL) and
saturated aqueous NaHCO3 solution (5 mL). The organic
layer was separated and the aqueous phase was extracted
with ether (10 mL). The combined organic solution was
washed with water (5 mL) and brine (5 mL), dried (MgSO4)
and concentrated. Flash column chromatography (silica
gel, 50% ether in hexanes) afforded nitrile **133** (53 mg,
80%) as a colorless oil: Rf = 0.44 (silica gel, 50% ether
in hexanes); [a]22D +10.3 (c 3.2, CHCl3); IR (thin film)
nmax 2926, 2855, 1503, 1457, 1381, 1250, 1179, 1072, 935,
833, 773, cm-1; 1H NMR (500 MHz, CDCl3) d 6.92 (s, 1 H,
SCH=C), 6.45 (s, 1 H, CH=CCH3), 5.18 (dd, J = 7.0, 6.5 Hz,
1 H, CH2CH=CCH3), 4.08 (dd, J = 6.5, 6.0 Hz, 1 H, CHOSi),
2.70 (s, 3 H, N=C(S)CH3), 2.60-2.53 (m, 1 H), 2.30-2.18
(m, 2 H), 2.11-1.97 (m, 2 H), 1.99 (s, 3 H, CH=CCH3), 1.67
(s, 3 H, CH2CH=CCH3) 1.67-1.45 (m, 4 H), 1.29 (d, J = 6.9

Hz, CHCH3), 0.88 (s, 9 H, SiC(CH3)3), 0.04 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 164.3, 153.0, 142.3, 135.5, 122.8, 122.4, 118.6, 114.9, 78.4, 35.3, 33.6, 31.1, 25.7, 25.4, 25.1, 23.2,

5   19.1, 18.1, 17.9, 13.9, -4.8, -5.1; FAB HRMS (NBA) m/e 433.2720, M + H+ calcd for C24H40N2OSSi 433.2709.

Synthesis of Aldehyde 75 as illustrated in Figure

17. Nitrile 133 (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to -78 °C. DIBAL (245 mL, 1 M

10   solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at -78 °C and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca 1 h). Methanol (150 mL) and aqueous HCl (150 mL, 1 N

15   solution) were sequentially added and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 5 mL) and the

20   combined organic solution was washed with brine (5 mL), dried (MgSO4), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde 75 (44 mg, 82%): Rf = 0.48 (silica gel, 50% ether in hexanes); [α]22D

25   +14.7 (c 1.7, CHCl3); IR (thin film) nmax 2915, 2859, 1721, 1500, 1455, 1381, 1251, 1183, 1070, 940, 832, 770 cm-1; 1H NMR (500 MHz, CDCl3) d 9.60 (d, J = 1.9 Hz, 1 H, CHO), 6.92 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH3), 5.16 (dd, J = 7.1, 7.0 Hz, 1 H, CH2CH=CCH3), 4.08 (dd, J =

7.0, 5.5 Hz, 1 H, CHOSi), 2.70 (s, 3 H, N=C(S)CH3), 2.36-
2.18 (m, 3 H), 2.07-2.01 (m, 2H), 1.99 (s, 3 H, CH=CCH3),
1.71-1.64 (m, 1 H), 1.66 (d, J = 1.0 Hz, 3 H, CH2CH=CCH3),
1.43-1.29 (m, 3 H), 1.08 (d, J = 7.0 Hz, 3 H, CH3CH); 0.88
(s, 9 H, SiC(CH3)3), 0.04 (s, 3 H, Si(CH3)2), -0.01 (s, 3
H, Si(CH3)2); 13C NMR (125.7 MHz, CDC13) d 205.0, 164.4,
153.1, 142.3, 135.9, 122.0, 118.6, 114.9, 78.8, 46.1,
35.3, 31.7, 30.2, 25.7, 25.1, 23.3, 19.1, 18.2, 13.8,
13.2, -4.8, -5.1; FAB HRMS (NBA) m/e 436.2717, M + H+
calcd for C24H41NO2SSi 436.2706.

**Synthesis of 12Z-Carboxylic Acids 119a and 119b as
illustrated in Figure 18.** Aldol Reaction of Keto Acid
76 with 12Z-aldehyde 75. A solution of keto acid 76 (365
mg, 1.21 mmol, 1.6 equiv) in THF (5.0 mL) was reacted with
12Z-aldehyde 75 (330 mg, 0.76 mmol, 1.0 equiv) according
to the same procedure as described above for the
condensation of 76 and 75 to afford, after similar
processing, geometrically pure 12Z-carboxylic acids 119a
(207 mg, 32%) and 119b (181 mg, 28%) and recovered 76.
12Z-carboxylic acid 119a: Rf = 0.56 (silica gel, 5% MeOH
in Methylene chloride); [a]22D -2.9 (c 0.8, CHC13); IR
(thin film) nmax 2933, 2854, 1708, 1464, 1385, 1249, 1187,
1079, 983, 830, 773 cm-1; 1H NMR (500 MHz, CDC13) d 6.92
(s, 1 H, SCH=C), 6.58 (s, 1 H, CH=CCH3), 5.15 (dd, J =
7.4, 7.1 Hz, 1 H, (CH3)C=CHCH2), 4.39 (dd, J = 6.7, 3.0
Hz, 1 H, (CH3)2CCHOSi), 4.11 (dd, J = 7.3, 5.7 Hz, 1 H,
CH2CHOSi), 3.74 (dd, J = 6.1, 1.8 Hz, 1 H, CH(CH3)CHOSi),
3.13 (dq, J = 7.0, 6.5 Hz, 1 H, C(O)CH(CH3)), 2.70 (s, 3

H, N=C(CH3)S), 2.44 (dd, J = 16.4, 3.1 Hz, 1 H, CH2COOH),
2.31 (dd, J = 16.4, 6.8 Hz, 1 H, CH2COOH), 2.28-2.04 (m, 3
H, CH2C(CH3)=CH, CH2C(CH3)=CHCH2), 1.94 (s, 3 H,
CH=C(CH3)), 1.96-1.86 (m, 1 H), 1.66 (s, 3 H,
CH2C(CH3)=CH), 1.47-1.31 (m, 4 H), 1.17 (s, 3 H, C(CH3)2),
1.12 (s, 3 H, C(CH3)2), 1.21-1.09 (m, 1 H), 1.08 (d, J =
6.8 Hz, 3 H, CH(CH3)), 0.90-0.85 (m, 30 H, CH(CH3), 3 x
SiC(CH3)3), 0.10 (s, 3 H, Si(CH3)2), 0.06 (s, 3 H,
Si(CH3)2), 0.05 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H,
Si(CH3)2), 0.02 (s, 3 H, Si(CH3)2), -0.02 (s, 3 H,
Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 218.2, 175.5,
165.0, 152.8, 143.4, 137.0, 121.6, 118.2, 114.5, 79.1,
73.1, 53.8, 44.4, 40.0, 39.2, 35.3, 32.4, 31.4, 26.2,
26.0, 25.8, 25.7, 23.5, 23.4, 18.8, 18.7, 18.4, 18.2,
16.8, 15.8, 13.9, -3.9, -4.0, -4.1, -4.6, -4.7, -5.0; FAB
HRMS (NBA/CsI) m/e 984.4427, M + Cs+ calcd for
C45H85NO6SSi3 984.4460. 12Z-carboxylic acid 119b: Rf =
0.65 (silica gel, 5% MeOH in Methylene chloride); [a]22D
+6.2 (c 0.6, CHCl3); IR (thin film) nmax 2933, 2854, 1708,
1459, 1386, 1249, 1074, 988, 830, 773 cm-1; 1H NMR (500
MHz, CDCl3) d 6.91 (s, 1 H, SCH=C), 6.45 (s, 1 H,
CH=CCH3), 5.12 (dd, J = 7.4, 6.9 Hz, 1 H, (CH3)C=CHCH2),
4.56 (dd, J = 6.1, 5.6 Hz, 1 H, (CH3)2CCHOSi), 4.07 (dd, J
= 7.6, 5.6 Hz, 1 H, CH2CHOSi), 3.85 (d, J = 8.4 Hz, 1 H,
CH(CH3)CHOSi), 3.10 (dq, J = 7.1, 7.0 Hz, 1 H,
C(O)CH(CH3)), 2.75 (s, 3 H, N=C(CH3)S), 2.43-2.10 (m, 4
H), 1.96-1.88 (m, 2 H), 1.91 (s, 3 H, CH=C(CH3)), 1.66 (s,
3 H, CH2C(CH3)=CH), 1.35-1.02 (m, 14 H, CH(CH3), 2 x CH2,
C(CH3)2, C(CH3)2, CH(CH3)), 0.92-0.80 (m, 30 H, 3 x

SiC(CH3)3, CH(CH3)), 0.09-0.01 (m, 18 H, 3 x Si(CH3)2);
13C NMR (125.7 MHz, CDC13) d 218.1, 174.2, 165.4, 152.3,
143.7, 137.1, 121.6, 117.9, 114.4, 78.9, 72.4, 53.8, 45.8,
40.4, 38.3, 35.6, 35.3, 32.3, 26.7, 26.3, 26.2, 26.0;
25.8, 25.7, 23.9, 23.3, 18.6, 18.5, 18.4, 17.1, 13.9,
13.4, -3.4, -3.6, -4.3, -4.6, -4.7, -4.9; FAB HRMS
(NBA/CsI) m/e 984.4430, M + Cs+ calcd for C45H85NO6SSi3
984.4460.

**Synthesis of 12Z-Hydroxy Acid 73 as illustrated in
Figure 18.** 12Z-carboxylic acid 119a (400 mg, 0.47 mmol)
was converted to 12Z-hydroxy acid 73 (253 mg, 73% yield)
according to the same procedure described above for 72
(Figure 14). 73: Yellow oil; Rf = 0.41 (silica gel, 5%
MeOH in Methylene chloride); [α]22D -10.4 (c 0.4, CHC13);
IR (thin film) nmax 3227, 2933, 2852, 1711, 1696, 1468,
1387, 1245, 1189, 1087, 986, 834, 773 cm-1; 1H NMR (500
MHz, CDC13) d 6.95 (s, 1 H SCH=C), 6.67 (s, 1 H,
CH=CCH3), 5.19 (dd, 1 H, J = 7.5, 7.0 Hz, CH3C=CHCH2),
4.41 (dd, J = 6.0, 3.5 Hz, 1 H, (CH3)2CCHOSi), 4.16 (dd, J
= 6.6, 6.5 Hz, 1 H, CH2CHOH), 3.78 (d, J = 6.9 Hz, 1 H,
CH(CH3)CHOSi), 3.13 (dq, J = 6.9, 6.6 Hz, 1 H,
C(O)CHCH3), 2.72 (s, 3 H, N=C(CH3)S), 2.47 (dd, J = 16.2,
3.9 Hz, 1 H, CH2COOH), 2.40-2.35 (m, 3 H, CH2C(CH3)=CH,
CH2COOH), 2.17-2.10 (m, 1 H, C(CH3)=CHCH2), 2.00 (s, 3 H,
CH=C(CH3)), 1.99-1.93 (m, 1 H, C(CH3)=CHCH2), 1.72 (s, 3
H, CH2C(CH3)=CH), 1.53-1.35 (m, 5 H), 1.19 (s, 3 H,
C(CH3)2), 1.14 (s, 3 H, C(CH3)2), 1.07 (d, J = 6.7 Hz, 3
H, CH(CH3)), 0.94-0.84 (m, 21 H, CH(CH3), SiC(CH3)3), 0.11

(s, 3 H, Si(CH3)2), 0.07 (s, 6 H, Si(CH3)2), 0.05 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 217.9, 174.8, 165.1, 152.3, 142.1, 139.4, 120.2, 118.5, 115.0, 73.2, 53.8, 44.5, 40.0, 39.1, 34.1, 32.4, 31.2, 26.2, 26.1, 25.9, 23.5, 23.3, 18.9, 18.6, 18.3, 18.1, 16.8, 16.0, 14.6, -3.9, -4.1, -4.2, -4.7; FAB HRMS (NBA/CsI) m/e 870.3632, M + Cs+ calcd for C39H71NO6SSi2 870.3595. **Synthesis of Hydroxy Acid 134 as illustrated in Figure 18.** 12Z-carboxylic acid 119b (200 mg, 0.24 mmol) was converted to 12Z-hydroxy acid 134 (123 mg, 71% yield) according to the procedure described above for 72 (Figure 14). 134: yellow oil; Rf = 0.45 (silica gel, 5% MeOH in Methylene chloride); [α]22D -8.1 (c 0.3, CHCl3); IR (thin film) nmax 3227, 2933, 2862, 1711, 1691, 1463, 1382, 1250, 1189, 1082, 986, 834, 773 cm-1; 1H NMR (500 MHz, CDCl3) d 6.96 (s, 1 H SCH=C), 6.61 (s, 1 H, CH=CCH3), 5.15 (dd, 1 H, J = 7.5, 7.0 Hz, CH3C=CHCH2), 4.55 (dd, J = 6.1, 3.5 Hz, 1 H, (CH3)2CCHOSi), 4.12 (dd, J = 8.0, 4.5 Hz, 1 H, CH2CHOH), 3.86 (d, J = 8.2 Hz, 1 H, CH(CH3)CHOSi), 3.12 (dq, J = 7.2, 7.0 Hz, 1 H, C(O)CHCH3), 2.75 (s, 3 H, N=C(CH3)S), 2.37-2.30 (m, 5 H, CH2C(CH3)=CH, CH2COOH, C(CH3)=CHCH2), 1.98 (s, 3 H, CH=C(CH3)), 1.94-1.89 (m, 1 H), 1.72 (s, 3 H, CH2C(CH3)=CH), 1.39-1.04 (m, 14 H, CH(CH3), CH(CH3), 2 x CH2, C(CH3)2), 0.95-0.84 (m, 21 H, SiC(CH3)3, CH(CH3)), 0.09 (s, 3 H, Si(CH3)2), 0.08 (s, 3 H, Si(CH3)2), 0.07 (s, 6 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 218.6, 174.0, 165.6, 152.0, 142.4, 139.4, 120.1, 118.0, 114.7, 72.4, 53.8, 45.8, 40.4, 38.4, 35.5, 34.0, 32.1, 26.4, 26.2, 26.0, 25.9, 23.8, 23.6, 18.5, 18.4,

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18.2, 17.2, 14.9, 13.2, -3.5, -3.7, -4.4, -4.8; FAB HRMS
(NBA/CsI) m/e 870.3574, M + Cs+ calcd for C39H71NO6SSi2
870.3595.

**Synthesis of Lactone 121 as illustrated in Figure
18.** Macrolactonization of 12Z-hydroxy acid 73. 12Z-
hydroxy acid 73 (8.1 mg, 0.011 mmol) was cyclized
according to the procedure described above for 73' (Figure
16) to afford lactone 121 (6.1 mg, 77%).

**Synthesis of Lactone 135 as illustrated in Figure
18.** Macrolactonization of 12Z-Hydroxy Acid 134.
The macrolactonization of 12Z-hydroxy acid 134 (5.0 mg,
0.007 mmol) to lactone 135 (3.7 mg, 76%) was carried out
according to the procedure described above for 73' (Figure
16). 135: Colorless oil; Rf = 0.83 (silica gel, 2% MeOH
in Methylene chloride); [α]22D -31.8 (c 0.1, CHC13); IR
(thin film) nmax 2931, 2860, 1736, 1690, 1461, 1384, 1360,
1296, 1249, 1084, 985, 832, 773 cm-1; 1H NMR (600 MHz,
CDC13) d 6.98 (s, 1 H, SCH=C), 6.45 (s, 1 H, CH=CCH3),
5.07-5.21 (m, 2 H, CH3C=CHCH2, CH2COOCH), 4.32 (dd, J =
6.8, 5.0 Hz, 1 H, CHOSi), 4.05 (d, J = 5.7 Hz, 1 H,
CHOSi), 3.17 (dq, J = 7.0, 6.8 Hz, 1 H, C(O)CHCH3), 2.70
(s, 3 H, N=C(CH3)S), 2.57-2.52 (m, 1 H), 2.29 (dd, J =
14.4, 4.6 Hz, 1 H, CH2COOCH), 2.27-2.13 (m, 1 H), 2.25
(dd, J = 14.5, 7.0 Hz, 1 H, CH2COO), 2.20-2.15 (m, 1 H),
2.14 (s, 3 H, CH=C(CH3)), 1.88-1.82 (m, 1 H), 1.57-1.52
(m, 2 H), 1.47-1.38 (m, 3 H), 1.30 (s, 3 H, C(CH3)2), 1.11
(d, J = 7.2 Hz, 3 H, CH(CH3)), 1.08 (s, 3 H, C(CH3)2),
0.91 (s, 9 H, SiC(CH3)3), 0.89-0.82 (bs, 12 H, SiC(CH3)3,

CH(CH3)), 0.11 (s, 3 H, Si(CH3)2), 0.09 (s, 3 H,
Si(CH3)2), 0.06 (s, 3 H, Si(CH3)2), -0.03 (s, 3 H,
Si(CH3)2); 13C NMR (150.9 MHz, CDC13) d 220.2, 170.9,
164.8, 153.1, 140.0, 137.6, 120.2, 118.9, 116.3, 79.3,
74.0, 53.3, 48.0, 41.2, 39.7, 34.9, 31.4, 31.3, 26.6,
26.1, 25.9, 25.3, 23.9, 19.0, 18.5, 18.4, 18.1, 16.2,
14.9, 13.8, -3.9, -4.4, -4.6, -4.9; FAB HRMS (NBA/CsI) m/e
852.3451, M + Cs+ calcd for C39H69NO5SSi2 852.3489.

**Synthesis of Ketone 69 as illustrated in Figure
19.** To a solution of aldehyde 87 (1.3 g, 4.53 mol) in
THF (20 mL) at -78 oC was added dropwise lithium tri-tert-
butoxyaluminohydride (4.98 mL, 1.0 M solution in THF, 4.98
mmol, 1.1 equiv). After 5 min, the reaction mixture was
brought up to 0 °C and stirred at that temperature for 15
min, before quenching with saturated aqueous solution of
sodium-potasium tartrate (25 mL). The aqueous phase was
extracted with ether (3 x 20 mL) and the combined organic
layer was dried (MgSO4), filtered and concentrated. The
crude primary alcohol so obtained was dissolved in
Methylene chloride (25 mL) and cooled to 0 °C. Et3N (2.5
mL, 15.85 mmol, 3.5 equiv), 4-DMAP (60 mg, 0.09 mmol, 0.02
equiv) and tert-butyldimethylsilyl chloride (2.0 g, 13.59
mmol, 3.0 equiv) were added. The reaction mixture was
allowed to stir at 0 °C for 2 h, then at 25 °C for 10 h.
MeOH (5 mL) was added and the solvents were removed under
reduced pressure. Ether (100 mL) was added followed by
saturated aqueous NH4Cl solution (25 mL) and the organic
phase was separated. The aqueous phase was extracted with

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ether (2 x 50 mL) and the combined organic solution was dried (MgSO4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 5% ether in hexanes) provided pure bis(silylether) 136 (1.26 g, 70% yield from 20): Rf = 0.67 (silica gel, 20% ether in hexanes); [a]22D -7.3 (c 1.8, CHCl3); IR (thin film) nmax 2941, 2856, 1701, 1466, 1388, 1252, 1095, 1024, 946, 832, 775 cm-1; 1H NMR (500 MHz, CDCl3) d 4.06 (dd, J = 8.0, 3.0 Hz, 1 H, CHOSi), 3.65-3.56 (m, 2 H, CH2OSi), 2.56 (dq, J = 18.5, 7.0 Hz, 1 H, CH2CH3), 2.46 (dq, J = 18.5, 7.0 Hz, 1 H, CH2CH3), 1.56-1.43 (m, 2 H, CH2CH2OSi), 1.11 (s, 3 H, C(CH3)2), 1.04 (s, 3 H, C(CH3)2), 0.98 (t, J = 7.0 Hz, 3 H, CH3CH2), 0.88 (s, 9 H, SiC(CH3)3), 0.87 (s, 9 H, SiC(CH3)3), 0.09 (s, 3 H, Si(CH3)2), 0.04 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H, Si(CH3)2), 0.02 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 215.5, 73.2, 59.9, 52.9, 37.1, 31.4, 25.9, 25.7, 22.0, 19.8, 18.2, 18.1, 7.6, -4.1, -4.2, -5.4, -5.5; FAB HRMS (NBA) m/e 403.3075, M + H+ calcd for C21H46O3Si2 403.3064.

Synthesis of tris(Silylethers) 137 and 138 as illustrated in Figure 19.. Aldol Reaction of Ketone 136 with Aldehyde 75. A solution of ketone 136 (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (94 mL, 0.67 mmol) was added to n-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0 ˚C] in THF (2.5 mL) at -78 ˚C. After stirring for 15 min at -

78 °C, the solution was allowed to warm to -40 °C over a period of 1 h. The reaction mixture was cooled to -78 °C, and a solution of aldehyde 8 (244 mg, 0.56 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78 °C, and then quenched by dropwise addition of saturated aqueous NH4Cl solution (2 mL). The aqueous phase was extracted with ether (3 x 5 mL) and the combined organic layer was dried (MgSO4) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products 137:138 (354 mg (85%) of ca 3:1 by 1H NMR). Separation of these diastereoisomers was carried out by preparative thin layer chromatography (silica gel, 20% ether in hexanes) leading to pure 137 (270 mg, 64%) and 138 (84 mg, 20%). 137: Colorless oil; Rf = 0.40 (silica gel, 20% ether in hexanes); [α]22D -17.5 (c 0.5, CHCl3); IR (thin film) nmax 3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775 cm-1; 1H NMR (500 MHz, CDCl3) d 6.89 (s, 1 H, SCH=C), 6.44 (s, 1 H, CH=CCH3), 5.12 (dd, J = 7.1, 7.0 Hz , 1 H, C(CH3)=CHCH2), 4.08 (dd, J = 6.8, 6.5 Hz, 1 H, (CH3)2CCHOSi), 3.89 (dd, J = 7.6, 2.7 Hz, 1 H, CH2CHOSi), 3.69-3.65 (m, 1 H, CH(CH3)CHOH), 3.59 (t, J = 7.5 Hz, 2 H, CH2OSi), 3.32-3.27 (m, 1 H, C(O)CH(CH3)), 2.68 (s, 3 H, N=C(CH3)S), 2.30-2.19 (m, 2 H, C(CH3)=CHCH2), 2.10-1.90 (m, 2 H, CH2C(CH3)=CH), 1.98 (s, 3 H, CH=C(CH3)), 1.65 (s, 3 H, C(CH3)=CHCH2), 1.80-1.46 (m, 5 H), 1.34-1.25 (m, 2 H), 1.19 (s, 3 H, C(CH3)2), 1.07 (s, 3 H, C(CH3)2), 1.01 (d, J = 6.8 Hz, 3 H, CH(CH3)), 0.89 (s, 18 H, 2 x SiC(CH3)3), 0.87 (s, 9 H,

SiC(CH3)3), 0.81 (d, J = 6.8 Hz, 3 H, CH(CH3)), 0.10 (s, 3
H, Si(CH3)2), 0.08 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H,
Si(CH3)2), 0.02 (s, 6 H, Si(CH3)2), -0.01 (s, 3 H,
Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 222.0, 164.1,
153.1, 142.4, 136.7, 121.3, 118.5, 114.7, 78.9, 74.7,
74.0, 60.3, 53.8, 41.2, 37.7, 35.9, 32.8, 32.5, 32.2,
26.0, 25.9, 25.8, 25.0, 24.9, 23.5, 22.8, 20.4, 19.0,
18.2, 18.1, 18.0, 15.2, 13.8, 9.5, -3.8, -4.2, -4.8, -5.1,
-5.4; FAB HRMS (NBA/CsI) m/e 970.4620, M + Cs+ calcd for
C45H87NO5SSi3 970.4667. 138: Colorless oil; Rf = 0.33
(silica gel, 20% ether in hexanes); IR (thin film) nmax
3490, 2932, 2873, 1683, 1463, 1385, 1249, 1089, 840, 775
cm-1; 1H NMR (500 MHz, CDCl3) d 6.90 (s, 1 H, SCH=C),
6.44 (s, 1 H, CH=CCH3), 5.16-5.12 (m, 1 H, C(CH3)=CHCH2),
4.09-4.05 (m, 1 H, (CH3)2CCHOSi), 3.65-3.58 (m, 3 H,
CH2CHOSi, CH2OSi), 3.42-3.38 (m, 1 H, CH(CH3)CHOH), 3.24-
3.19 (m, 1 H, C(O)CH(CH3)), 2.69 (s, 3 H, N=C(CH3)S),
2.31-2.18 (m, 2 H, C(CH3)=CHCH2), 1.98 (s, 3 H,
CH=C(CH3)), 1.99-1.88 (m, 2 H, CH2C(CH3)=CH), 1.67 (s, 3
H, C(CH3)=CHCH2), 1.55-1.40 (m, 5 H), 1.35-1.25 (m, 2 H),
1.20 (s, 3 H, C(CH3)2), 1.13 (s, 3 H, C(CH3)2), 1.09 (d, J
= 7.0 Hz, 3 H, CH(CH3)), 0.95 (d, J = 7.0 Hz, 3 H,
CH(CH3)), 0.88 (s, 18 H, 2 x SiC(CH3)3), 0.87 (s, 9 H,
SiC(CH3)3), 0.10 (s, 3 H, Si(CH3)2), 0.05 (s, 3 H,
Si(CH3)2), 0.04 (s, 3 H, Si(CH3)2), 0.03 (s, 6 H,
Si(CH3)2), -0.01 (s, 3 H, Si(CH3)2); FAB HRMS (NBA) m/e
838.5653, M + Cs+ calcd for C45H87NO5SSi3 838.5691.

Synthesis of tetra(silylether) 139 as illustrated

in Figure 19.. Compound 137 (275 mg, 0.33 mmol) was
dissolved in Methylene chloride (5.0 mL), cooled to 0 °C
and treated with 2,6-lutidine (76 mL, 0.66 mmol, 2.0
equiv) and tert-butyldimethylsilyl
trifluoromethanesulfonate (88 mL, 0.39 mmol, 1.2 equiv).
After stirring for 2 h at 0 °C, the reaction mixture was
quenched with aqueous HCl (5 mL, 1.0 N solution) and the
aqueous phase was extracted with Methylene chloride (3 x 5
mL). The combined organic solution was washed with brine
(5 mL), dried (MgSO4) and concentrated under reduced
pressure. Purification by flash column chromatography
(silica gel, 3% ether in hexanes) provided
tetra(silylether) 139 (300 mg, 96%) as a colorless oil.
139: Rf = 0.56 (silica gel, 10% ether in hexanes); [a]22D
-10.8 (c 0.5, CHCl3); IR (thin film) nmax 2919, 2872,
1690, 1461, 1384, 1361, 1249, 1085, 985, 838, 773, 732,
667 cm-1; 1H NMR (500 MHz, CDCl3) d 6.88 (s, 1 H, SCH=C),
6.43 (s, 1 H, CH=CCH3), 5.13 (dd, J = 7.1, 7.0 Hz, 1 H,
C(CH3)=CHCH2), 4.08 (dd, J = 6.8, 6.7 Hz, 1 H,
(CH3)2CCHOSi), 3.89 (dd, J = 7.6, 2.7 Hz, 1 H, CH2CHOSi),
3.77 (dd, J = 6.7, 1.0 Hz, 1 H, CH(CH3)CHOSi), 3.67-3.62
(m, 1 H, CH2OSi), 3.58-3.53 (m, 1 H, CH2OSi), 3.14 (dd, J
= 6.8, 6.7 Hz, 1 H, C(O)CH(CH3)), 2.68 (s, 3 H,
N=C(CH3)S), 2.29-2.17 (m, 2 H, C(CH3)=CHCH2), 1.98 (s, 3
H, CH=C(CH3)), 1.97-1.89 (m, 2 H, CH2C(CH3)=CH), 1.64 (s,
3 H, C(CH3)=CHCH2) 1.50-1.45 (m, 5 H), 1.34-1.23 (m, 2 H),
1.20 (s, 3 H, C(CH3)2), 1.02 (d, J = 6.8 Hz, 3 H,
CH(CH3)), 1.00 (s, 3 H, C(CH3)2), 0.88-0.86 (m, 39 H,
CH(CH3), 4 x SiC(CH3)3), 0.08 (s, 3 H, Si(CH3)2), 0.07 (s,

3 H, Si(CH3)2), 0.04 (s, 3 H, Si(CH3)2), 0.03 (s, 3 H,
Si(CH3)2), 0.02 (s, 6 H, Si(CH3)2), 0.01 (s, 3 H,
Si(CH3)2), -0.02 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz,
CDC13) d 218.2, 164.2, 153.2, 142.4, 136.6, 121.5, 118.5,
114.9, 78.8, 77.3, 73.9, 60.9, 53.6, 44.9, 38.8, 37.9,
35.2, 32.4, 30.9, 26.2, 26.1, 25.9, 24.4, 23.4, 19.2,
19.1, 18.5, 18.3, 18.2, 18.1, 17.5, 13.9, -3.7, -3.8, -
4.0, -4.7, -4.9, -5.2, -5.3; FAB HRMS (NBA) m/e 952.6515,
M + H+ calcd for C51H101NO5SSi4 952.6556.

**Synthesis of Alcohol 140 as illustrated in Figure
19..** Alcohol 140 (200 mg, 85%) was obtained from
compound 139 (264 mg, 0.28 mmol) according to the
procedure described above for 102. 140: Colorless oil; Rf
= 0.25 (silica gel, 20% ether in hexanes); [a]22D -9.3 (c
0.2, CHC13); IR (thin film) nmax 3392, 2939, 2865, 1689,
1463, 1378, 1357, 1252, 1083, 988, 867, 835, 772, 730 cm-
1; 1H NMR (500 MHz, CDC13) d   6.90 (s, 1 H, SCH=C), 6.44
(s, 1 H, CH=CCH3), 5.14 (dd, J = 7.0, 6.9 Hz , 1 H,
C(CH3)=CHCH2), 4.10-4.05 (m, 2 H, (CH3)2CCHOSi, CH2CHOSi),
3.78 (dd, J = 7.0, 1.0 Hz, 1 H, CH(CH3)CHOSi), 3.63 (t, J
= 7.0 Hz , 2 H, CH2OH), 3.11 (dd, J = 7.0, 6.8 Hz, 1 H,
C(O)CH(CH3)), 2.70 (s, 3 H, N=C(CH3)S), 2.27-2.19 (m, 2 H,
C(CH3)=CHCH2), 1.99 (d, J = 1.0 Hz, 3 H, CH=C(CH3)), 2.10-
1.90 (m, 2 H, CH2C(CH3)=CH), 1.65 (s, 3 H, C(CH3)=CHCH2),
1.50-1.39 (m, 2 H), 1.36-1.29 (m, 3 H), 1.21 (s, 3 H,
C(CH3)2), 1.20-1.10 (m, 2 H), 1.05 (s, 3 H, C(CH3)2), 1.04
(d, J = 6.8 Hz, 3 H, CH(CH3)), 0.91-0.87 (m, 30 H,
CH(CH3), 3 x SiC(CH3)3), 0.11 (s, 3 H, Si(CH3)2), 0.07 (s,

3 H, Si(CH3)2), 0.06 (s, 6 H, Si(CH3)2), 0.04 (s, 3 H, Si(CH3)2), -0.01 (s, 3 H, Si(CH3)2); 13C NMR (125.7 MHz, CDCl3) d 219.5, 164.2, 153.1, 142.4, 136.6, 121.5, 118.5, 114.8, 78.8, 77.4, 72.9, 60.1, 53.6, 45.8, 44.9, 38.6, 38.2, 35.2, 32.4, 30.6, 26.1, 25.9, 24.7, 23.4, 19.1, 18.4, 18.1, 18.0, 17.6, 15.5, 13.8, -3.7, -3.8, -4.0, -4.7, -5.1; FAB HRMS (NBA/CsI) m/e 970.4694, M + Cs+ calcd for C45H87NO5SSi3 970.4667.

Synthesis of Aldehyde 141 as illustrated in Figure 19. Oxidation of Alcohol 140. To a solution of oxalyl chloride (54 mL, 0.61 mmol, 2.0 equiv) in Methylene chloride (5.0 mL) was added dropwise DMSO (86 mL, 1.21 mmol, 4.0 equiv) at -78 °C. After stirring for 15 min at -78 °C, a solution of alcohol 73 (255 mg, 0.305 mmol, 1.0 equiv) in Methylene chloride (2.0 mL) was added dropwise at -78 °C over a period of 5 min. The solution was stirred at -78 °C for 30 min, and then Et3N (250 mL, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min and then ether (20 mL) was added, followed by saturated aqueous NH4Cl solution (10 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 10 mL). The combined organic solution was dried (MgSO4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde 141 (241 mg, 95%) as a colorless oil. 141: Rf = 0.47 (silica gel, 20% ether in hexanes); [a]22D -12.0 (c 0.1, CHCl3); IR (thin

film) nmax 2943, 2849, 1725, 1690, 1461, 1384, 1249, 1079,
985, 832, 773 cm-1; 1H NMR (500 MHz, CDC13) d 9.74 (m, 1
H, CHO), 6.89 (s, 1 H, SCH=C), 6.43 (s, 1 H, CH=CCH3),
5.14 (dd, J = 7.1, 7.0 Hz, 1 H, C(CH3)=CHCH2), 4.48-4.44
(m, 1 H, (CH3)2CCHOSi), 4.07 (dd, J = 6.1, 5.3 Hz, 1 H,
CH2CHOSi), 3.75 (dd, J = 7.4, 1.0 Hz, 1 H, CH(CH3)CHOSi),
3.11 (dd, J = 7.0, 6.7 Hz, 1 H, C(O)CH(CH3)), 2.69 (s, 3
H, N=C(CH3)S), 2.50 (ddd, J = 16.6, 4.5, 1.0 Hz, 1 H,
CH2CHO), 2.37 (ddd, J = 16.6, 3.2, 1.0 Hz, 1 H, CH2CHO),
2.28-2.16 (m, 2 H, C(CH3)=CHCH2), 1.97 (s, 3 H,
CH=C(CH3)), 1.97-1.89 (m, 2 H, CH2C(CH3)=CH), 1.64 (s, 3
H, C(CH3)=CHCH2), 1.50-1.25 (m, 5 H), 1.22 (s, 3 H,
C(CH3)2), 1.05 (s, 3 H, C(CH3)2), 1.01 (d, J = 6.9 Hz, 3
H, CH(CH3)), 0.89-0.84 (m, 30 H, CH(CH3), 3 x SiC(CH3)3),
0.08 (s, 3 H, Si(CH3)2), 0.04 (s, 6 H, Si(CH3)2), 0.03 (s,
3 H, Si(CH3)2), 0.02 (s, 3 H, Si(CH3)2), -0.02 (s, 3 H,
Si(CH3)2); 13C NMR (125.7 MHz, CDC13) d 218.5, 201.0,
164.3, 153.2, 142.7, 136.7, 121.5, 118.5, 114.8, 78.9,
77.7, 71.3, 53.4, 45.1, 38.7, 35.3, 32.5, 30.7, 26.2,
25.9, 25.8, 24.1, 23.5, 19.1, 18.7, 18.6, 18.5, 17.7,
15.6, 13.9, -3.6, -3.7, -4.1, -4.5, -4.7, -5.0; FAB HRMS
(NBA) m/e 836.5500, M + H+ calcd for C45H85NO5SSi3
836.5535.

**Synthesis of Carboxylic Acid 119 as illustrated in
Figure 19.** Oxidation of Aldehyde 141. Aldehyde 141
(224 mg, 0.29 mmol), tBuOH (5.0 mL), isobutylene (5.0 mL,
2 M solution in THF, 10.0 mmol), H2O (1.0 mL), NaClO2 (90
mg, 0.86 mmol, 3.0 equiv) and NaH2PO4 (60 mg, 0.43 mmol,

1.5 equiv) were combined and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 6% MeOH in Methylene chloride) to afford carboxylic acid 52 (220 mg, 90%) whose spectroscopic data were identical to those exhibited by 119 obtained above.

Selected physical data for compound 158: 1H NMR (400 MHz, CDCl3) d 6.95 (s, 1 H, ArH), 6.59 (s, 1 H, ArCH=C(CH3)), 5.44 (ddd, J = 10.5, 10.5, 4.5 Hz, 1 H, CH=CHCH2), 5.36 (ddd, J = 10.5, 10.5, 5.0 Hz, 1 H, CH=CHCH2), 5.28 (d, J = 9.4 Hz, 1 H, CO2CH), 4.23 (d, J = 11.1 Hz, 1 H, (CH3)2CCH(OH)), 3.72 (m, 1 H, CHOH(CHCH3)), 3.43-3.37 (m, 1 H, OH), 3.14 (q, J = 6.7 Hz, 1 H, CH3CH(C=O)), 3.05 (bs, 1 H, OH), 2.72-2.63 (m, 1 H), 2.69 (s, 3 H, CH3Ar), 2.48 (dd, J = 14.8, 11.3 Hz, 1 H, CH2COO), 2.33 (dd, J = 14.8, 2.0 Hz, 1H, CH2COO), 2.30-2.13 (m, 2 H) 2.07 (s, 3 H, ArCH=CCH3), 2.07-1.98 (m, 1 H), 1.80-1.60 (m, 2H), 1.32 (s, 3 H, C(CH3)2), 1.36-1.13 (m, 3H), 1.17 (d, J = 6.8 Hz, 3 H, CH3CH(C=O)), 1.06 (s, 3 H, C(CH3)2), 0.99 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3) d 220.6, 170.4, 165.0 151.9, 138.7, 133.4, 125.0, 119.4, 115.8, 78.4, 74.1, 72.3, 53.3, 41.7, 39.2, 38.5, 32.4, 31.7, 27.6, 27.4, 22.7, 19.0, 18.6, 15.9, 15.5, 13.5; IR (thin film) $n$max 3453, 2929, 1733, 1686, 1506, 1464, 1250, 978 cm-1; [a]22D -80.2 (c 1.36, CHCl3); HRMS (FAB), calcd for C26H39CsNO5S (M + Cs+) 610.1603, found 610.1580.

Synthesis of of aldehyde 149 as illustrated in Figure 21

Step 1) A solution of (R)-3-bromo-2-methyl-1-propanol (Aldrich) (6.50 g, 42.4 mmol, 1.0 equiv.) in DMF (30 mL) at 0 oC was treated with t-butylchlorodimethylsilane (8.23 g, 54.6 mmol, 1.3 equiv.) and imidazole (4.32 g, 63.6 mmol, 1.5 equiv.). After stirring for 90 min at 0 oC, the reaction mixture was diluted with Et2O (250 mL) and poured in a 1 M HClaq. solution (150 mL). The organic phase was separated, washed with a 1 M HClaq. solution (2 x 150 mL), brine (150 mL), dried over MgSO4 and concentrated in vacuo. Flash chromatography (silica gel, 4% Et2O in hexane) afforded 11.2 g (99% yield) of pure compound as a colorless oil.

Step 2) A solution of above compound (11.2 g, 42.0 mmol, 1.0 equiv.) in acetone (200 mL) was treated with sodium iodide (18.9 g, 126 mmol, 3.0 equiv.) and refluxed for 15 h. The reaction mixture was then diluted with a 1:1 (v/v) solution of Et2O/ hexane (400 mL) and poured in a H2O (250 mL). The organic phase was separated, washed with brine (2 x 250 mL), dried over MgSO4 and concentrated in vacuo. Flash chromatography (silica gel, 4% Et2O in hexane) afforded 12.7 g (96% yield) of pure product as a colorless oil.

Step 3) A 0.01 M Li_2CuCl_4 solution in THF was prepared by mixing LiCl (85 mg, 2.0 mmol, 2.0 equiv.) and CuCl2 (136 mg, 1.0 mmol, 1.0 equiv.) in THF (100 mL). Above compound

made in step 2 (12.7 g, 40.44 mmol, 1.0 equiv.) was
dissolved in THF (25 mL), cooled to 0 oC and treated with
a solution of 3-butenylmagnesium bromide (0.5 M in THF,
100 mL, 50.0 mmol, 1.25 eqiv.), followed by the Li2CuCl4
solution (40.0 mL, 0.40 mmol, 0.01 equiv.). The reaction
mixture was stirred at 0 oC for 1 h then diluted with Et2O
(500 mL) and poured in a 1 M HClaq. (250 mL). The organic
phase was separated, washed with brine (2 x 250 mL), dried
over MgSO4 and concentrated in vacuo. Flash
chromatography (silica gel, 4% Et2O in hexane) afforded
9.3 g (93% yield) of olefin 1003 as a colorless oil.
Step 4) Olefin made in step 3 (4.0 g, 16.4 mmol) was
cooled to -78 oC. A gentel stream of ozone was passed
through this solution until it turned deep blue. The
reaction mixture was then allowed to warm up to room
temperature and excess ozone was discharged by sparging
argon through the solution. The reaction mixture was then
treated with Me2S (20 mL), Et3N (10 mL) and MeOH (20 mL).
This mixture was stirred at 23 oC for 1 h then diluted
with Et2O (300 mL) and poured in a 1M HClaq. (250 mL).
The organic phase was separated, washed with 1 M HClaq. (2
x 250 mL), dried over MgSO4 and concentrated in vacuo.
Flash chromatography (silica gel, 8% Et2O in hexane)
afforded 3.9 g (96% yield) of a pure colorless oil of
compound 149.

**Synthesis of phosphonium resin 147 as illustrated
in Figure 21**
Step 1) Alkylation of Merrifield Resin: A solution of

1,4-butanediol (7.18 g, 80.0 mmol, 5.0 equiv.) in DMF
(600 mL) was cooled to 0 oC and sodium hydride (60 %, 3.20
g, 80.0 mmol, 5.0 equiv.) was added. The reaction mixture
was stirred at 0 oC for 2 h and Merrifield resin (40.0 g,
16.0 mmol, 1.0 equiv.) followed by n-Bu4NI (0.58 g, 1.60
mmol, 0.1 equiv.) were added. The reaction mixture was
stirred at 23 oC for 20 h, then poured into a frit and the
polymer was washed with MeOH (2 x 500 mL), DMF (500 ml),
H2O at 80 oC (500 mL), DMF (500 ml), MeOH (500 mL), CH2Cl2
(500 mL), Et2O (2 x 300 mL). The resin was dried under
high vaccum to a constant weight of 40.8 g.
Step 2) Conversion of alcohol resin. A suspension of
resin from above step 1 (40.8 g, 16.0 mmol, 1.0 equiv.) in
CH_2Cl_2 (700 mL) at 23 oC was treated with Ph3P (20.9 g,
80.0 mmol, 5.0 equiv.), imidazole (6.46 g, 80.0 mmol, 5.0
equiv.) and iodine (16.0 g, 64.0 mmol, 4.0 equiv.). The
reaction mixture was stirred at 23 oC for 3 h then poured
into a frit and the polymer was washed with CH2Cl2 (500
mL), MeOH (500 mL), CH2Cl2 (500 mL), MeOH (500 mL),
CH2Cl2 (500 mL), Et2O (2 x 300 mL). The resin was dried
under high vaccum to a constant weight of 42.6 g.
Step 3) Reaction of iodo resin formed in step 2 with Ph_3P.
A suspension of iodo resin (42.6 g, 16.0 mmol, 1.0 equiv.)
in DMF (200 mL) at 23 oC was treated with Ph3P (41.9 g,
160 mmol, 10 equiv.). The reaction mixture was stirred at
90 oC for 12 h then poured into a frit and the polymer was
washed with DMF at 80 oC (3 x 500 mL), CH2Cl2 (500 mL),
DMF (500 mL), Et2O (3 x 500 mL). The resin was dried
under high vaccum to a constant weight of 46.61 g.

Synthesis of Ylide resin 148 as illustrated in Figure 21 Deprotonation of Phosphonim resin 147: A suspension of resin 147 (15.0 g, 5.11 mmol, 1.0 equiv.) in a mixture of DMSO (50 mL) THF (35 mL) at 23 oC was treated with a 1 M solution of NaHMDS in THF (15.3 mL, 15.3 mmol, 3.0 equiv.). The reaction mixture was stirred at 23 oC for 12 h then canulated into a Schlenk frit and the polymer was washed under argon with THF (3 x 100 mL).

Synthesis of resin 150 as illustrated in Figure 21 Wittig reaction of ylide resin 148 with aldehyde 149 (vida supra). A solution of aldehyde 149 (2.50 g, 10.22 mmol, 2.0 equiv.) in THF (25 mL) was cooled at -78 oC and added to the freshly prepared resin 148 (5.11 mmol, 1.0 equiv.) via canula. The resulting suspension was shaken at 23 oC for 3h and the supernatant was filtered off. The polymer was washed with THF (100 ml), MeOH (100 mL), CH2Cl2 (100 mL), MeOH (100 mL), CH2Cl2 (100 mL), Et2O (2 x 100 mL). The resin was dried under high vaccum to a constant weight of 14.12 g.

Synthesis of resin 145 as illustrated in Figure 21 Step 1) Desilylation of resin 150 with HF.Pyridine complex. Resin 150 (14.0 g, 5.05 mmol, 1.0 equiv.) was suspended in THF (135 mL) and treated at 0 oC with HF.Pyridine complex (15 mL). The mixture was allowed to warm to 23 oC and shaken for 12 h. The suspension was poured into a frit and the polymer was filtered, washed

with THF (100 mL), CH2Cl2 (100 mL), MeOH (100 mL), CH2Cl2 (100 mL), Et2O (2 x 100 mL) and dried under high vaccum to give 13.42 g of deprotected resin.

Step 2) Swern oxidation of deprotected resin. To an Oxalyl Chloride (2.56 g, 1.76 mL, 20.0 mmol, 4.0 equiv.) solution in CH2Cl2 (50 mL) at -78 oC, was added dropwise DMSO (3.12 g, 2.84 mL, 40.0 mmol, 8.0 equiv.). The solution was stirred at -78 oC for 1 h and canulated into a suspension of resin (13.26 g, 5.0 mmol, 1.0 equiv.) in CH2Cl2 , previously cooled to -78 oC. The resulting mixture was stirred for an additional hour and treated with Et3N (6.25 g, 8.0 mL, 62.5 mmol, 12.5 equiv.), allowed to warm to 23 oC and stirred for 1h. The mixture was filtered and the polymer washed succesively with CH2Cl2 (250 mL), MeOH (250 mL), CH2Cl2 (250 mL), Et2O (2 x 300 mL), dried under high vaccum to afford 13.25 g of resin 145.

Synthesis of resin 151 as illustrated in Figure 21
Step 1) Enolate formation. To a precooled solution of LDA (6.60 mmol, 4.4 equiv.) obtained by treating Diisopropyl amine (0.92 ml, 6.60 mmol, 4.4 equiv.) in THF (25 mL) at 0 oC with n-butyllithium (1.6 M solution in THF, 4.12 mL, 6.60 mmol, 4.4 equiv.) was added a solution of ketoacid 144 (vida supra) (0.93 g, 3.0 mmol, 2.0 equiv.) in THF (25 mL) at -78 oC via canula. The solution was allowed to warm to -40 oC and stirred for 1h.

Step 2) Aldol reaction. A suspension of resin 145(4.0 g, 1.50 mmol, 1.0 equiv.), ZnCl2 (1.0 M solution in Et2O, 3.0

mL, 3.0 mmol, 2.0 equiv.) in THF (25 mL), was treated at -78 oC with the enolate solution described above. The suspension was allowed to warm to -40 oC, stirred for 2 h, quenched with saturated NH4Claq (8 mL) and neutralised at 23 oC with AcOH (0.76 mL, 13.2 mmol, 8.8 equiv). The mixture was poured into a frit, the polymer was washed with THF (100 mL), Et2O (100 mL), CH2C12 (100 mL), H2O (100 mL), MeOH (100 mL), CH2C12 (100 mL), 1% TFA v/v in CH2C12 (3x75 mL), CH2C12 (2x100 mL), Et2O (2x100 mL) and dried under vaccum to afford 1.96 of resin 151.

Synthesis of resin 152 as illustrated in Figure 21.
Esterification of resin 151 with alcohol 143. A mixture of resin 151 (1.40 g, 0.46 mmol, 1.0 equiv.), alcohol 143 (vida supra) (0.49 g, 2.31 mmol, 5.0 equiv.), 4-DMAP (0.32 g, 2.31 mmol, 5.0 equiv.) and DCC (0.46 g, 2.31 mmol, 5.0 equiv.) in CH2C12 (10 mL) was shaken al 23 oC for 15 h. The polymer was filtered, washed with CH2C12 (2x50 mL), MeOH (2x50 mL), CH2C12 (2x50 mL), Et2O (2x50 mL) and dried under vaccum to afford 1,48 g of resin 152.

Synthesis of 154 as illustrated in Figure 21
Metathesis of resin 152. A suspension of resin 152 (500 mg) in CH2C12 (40 mL) was treated with bis(tricyclohexylphosphine)benzylidine ruthenium dichloride (RuCl2(=CHPh)(PCy3)2) (20 mg) and stirred at 23 oC for 48 h. The polymer was filtered and the filtrate was evaporated and purified by preparative thin layer chromatography (silicagel, 20 % ethyl acetate in hexanes)

to give compounds 154, 155, 156, 157 = ca: 3:3:1:3. 52 %
yield from the calculated loading of heterocycle in resin
152.

5   **Synthesis of 157 and 158 as illustrated in Figure
21**
trans-Dihydroxy Lactone 157 and 158. Desilylation of
Compound 141 and 155. Silyl ether 141 or 155 (44 mg,
0.074 mmol) was treated with a freshly prepared solution
10   of 20% (v/v) trifluoroacetic acid (TFA)-CH2Cl2 (7.4 mL,
0.01 M) to yield, after flash column chromatography
(silica gel, 50% EtOAc in hexanes), trans-dihydroxy ester
157 or 158 (33 mg, 93%)

15   **Synthesis of Eposterones 159 and 1 as illustrated
in Figure 21.** Epoxidation of cis-Hydroxy Lactone 157
and 158. To a solution of cis-hydroxy lactone 157 and 158
(19 mg, 0.039 mmol) in acetonitrile (390 mL, 0.1 M) is
added a 0.0004 M aqueous solution of disodium salt of
20   ethylenediaminetetraacetic acid (Na2EDTA, 200 mL, 0.2 M)
and the reaction mixture is cooled to 0 oC. Excess of
1,1,1-trifluoroacetone (80 mL, 0.5 M) is added, followed
by a portionwise addition of Oxone® (120 mg, 0.20 mmol,
5.0 equiv) and NaHCO3 (26 mg, 0.31 mmol, 8.0 equiv) with
25   stirring, until the disappearance of starting material is
detected by TLC. The reaction mixture is then directly
passed through silica gel and eluted with 50% EtOAc in
hexanes. Purification by preparative thin layer
chromatography (250 mm silica gel plate, 70% EtOAc in

hexanes) provides the diastereomeric eposterones 159 or 1 (epothilone A).

Synthesis of alcohol 163. Allylboration of Aldehyde 162 as illuststrated in Figure 25. Aldehyde 162 (1.0 equiv) was dissolved in anhydrous ether (0.3 M) and the solution was cooled to -100 °C. (+)-Diisopinocampheylallyl borane (1.2 equiv in pentane, prepared from (-)-Ipc₂BOMe and 1.0 equiv of allyl magnesium bromide) was added dropwise under vigorous stirring, and the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol was added at -100 °C, and the reaction mixture was allowed to warm up to room temperature. Amino ethanol (10.0 equiv) was added and stirring was continued for 15 h. The work-up procedure was completed by the addition of saturated aqueous NH₄Cl solution, extraction with EtOAc and drying of the combined organic layers with MgSO₄. Filtration, followed by evaporation of the solvents under reduced pressure and flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol 163 (91%).

Synthesis of hydroxy Esters 164 and 165. EDC Coupling of Carboxylic Acids 45 and 46 and Alcohol 163 as illustrated in Figure 25. The crude mixture of keto acids 45 and 46 (1.0 equiv; vida supra), 4-(dimethylamino)pyridine (4-DMAP, 1.5 equiv), and alcohol

163 (2.0 equiv) in CH_2Cl_2 (2.0 M) was cooled to 0 °C and then treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 1.5 equiv). The reaction mixture was stirred at 0 °C for 2 h and then at 25 °C for 12 h. The work-up procedure was completed by the addition of saturated aqueous $NHCO_3$ solution, extraction with ether and drying of the combined organic layers with $MgSO_4$. Evaporation of the solvents followed by flash column chromatography (silica gel, 15% EtOAc in hexanes) resulted in pure hydroxy esters 164 (49% from keto acid 8) and 165 (33% from keto acid 8).

Synthesis of hydroxy lactones 166 and 167 as illustrated in Figure 26. Cyclization of Diene 164 via Olefin Metathesis. To a solution of diene 164 (1.0 equiv) in CH_2Cl_2 (0.0015 M) was added bis(tricyclohexylphosphine)benzylidine ruthenium dichloride ($RuCl_2(=CHPh)(PCy_3)_2$, 0.2 equiv) and the reaction mixture was allowed to stir at 25 °C for 20 h. After the completion of the reaction was established by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give hydroxy lactones 166 (40%) and 167 (29%).

Synthesis of cis-Dihydroxy Lactone 168 as illustrated in Figure 26. Desilylation of Compound 166. Silyl ether 166 (1.0 equiv) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-CH_2Cl_2 (0.01 M) at 0 °C. The reaction mixture was

stirred at 0 °C for 30 min (completion of the reaction by TLC). The work-up procedure was completed by the addition of saturated aqueous NHCO$_3$ solution, extraction with EtOAc and drying of the combined organic layers with MgSO$_4$. Evaporation of the solvents followed by flash column chromatography (silica gel, ether) resulted in pure cis-dihydroxy lactone 168 (89%). Rf = 0.21 (silica gel, 50% EtOAc in hexanes); [α]$^{22}_D$ -46.5 (c 0.71, CHCl$_3$); IR (thin film) n$_{max}$ 3406, 2930, 1733, 1686, 1584, 1251, 733 cm-1; 1H NMR (500 MHz, CDCl3) δ 7.47 (s, 1 H, ArH), 6.31 (s, 1 H, ArCH=C(CH3)), 5.43 (ddd, J = 10.5, 10.5, 4.0 Hz, 1 H, CH=CHCH2), 5.36 (ddd, J = 10.5, 10.5, 4.5 Hz, 1 H, CH=CHCH2), 5.28 (d, J = 9.5 Hz, 1 H, CO2CH), 4.15 (d, J = 11.0 Hz, 1 H, (CH3)2CCH(OH)), 3.72 (m, 1 H, CHOH(CHCH3)), 3.11 (qd, J = 7.0, 2.5 Hz, 1 H, CH3CH(C=O)), 3.02 (bs, 2 H, OH), 2.70-2.62 (m, 1 H), 2.50 (dd, J = 15.5, 11.0 Hz, 1 H, CH2COO), 2.43 (s, 3 H, CH3Ar), 2.38 (dd, J = 15.5, 2.5 Hz, 1H, CH2COO), 2.26-2.13 (m, 2 H), 2.07-1.98 (m, 1 H), 1.98 (s, 3 H, ArCH=CCH3), 1.80-1.60 (m, 2H), 1.31 (s, 3 H, C(CH3)2), 1.37-1.13 (m, 3H), 1.17 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.07 (s, 3 H, C(CH3)2), 0.98 (d, J = 7.0 Hz, 3 H, CH3CHCH2); 13C NMR (150.9 MHz, CDCl3) d 220.3, 170.3, 160.9, 137.8, 137.4, 135.6, 133.5, 124.8, 115.9, 78.3, 74.2, 72.6, 53.0, 42.0, 39.0, 38.5, 32.4, 31.6, 27.6, 27.5, 22.5, 19.3, 15.9, 15.6, 13.8, 13.7; HRMS (FAB), calcd for C26H40NO6 (M + H+) 462.2856, found 462.2844.

Synthesis of trans-Dihydroxy Lactone 169.
Desilylation of Compound 167 as illustrated in
Figure 26. Silyl ether 167 (1.0 equiv) was treated with
a freshly prepared solution of 20% (v/v) trifluoroacetic
acid-CH2C12 (0.01 M) at 0 °C. The reaction mixture was
stirred at 0 °C for 60 min (completion of the reaction by
TLC). The work-up procedure was completed by the addition
of saturated aqueous NHCO3 solution, extraction with EtOAc
and drying of the combined organic layers with MgSO4.
Evaporation of the solvents followed by flash column
chromatography (silica gel, ether) resulted in pure trans-
dihydroxy ester 169 (95%). Rf = 0.22 (silica gel, 50%
EtOAc in hexanes); $[\alpha]22D$ -37.9 (c 0.70; CHCl3); IR
(film) nmax 3400, 2933, 1733, 1688, 1583, 1466, 1251, 756
cm-1; 1H NMR (500 MHz, CDC13) d 7.49 (s, 1 H, ArH), 6.29
(s, 1 H, ArCH=CCH3), 5.50 (ddd, J = 15.0, 7.5, 7.5 Hz, 1
H, CH=CHCH2), 5.37 (dd, J = 5.5, 5.5 Hz, 1 H, CO2CH), 5.34
(ddd, J = 15.0, 7.5, 7.5 Hz, 1 H, CH=CHCH2), 4.19 (d, J =
10.0, 3.0 Hz, 1 H, (CH3)2CCH(OH)), 3.73 (dd, J = 5.5, 2.5
Hz, 1 H, CHOH(CHCH3)), 3.26 (qd, J = 7.0, 6.5 Hz, 1H,
CH3CH(C=O)), 3.01 (bs, 1 H, OH), 2.86 (bs, 1 H, OH), 2.55
(dd, J = 15.5, 10.0 Hz, 1 H, CH2COO), 2.49 (dd, J = 15.5,
3.0 Hz, 1 H, CH2COO), 2.45 (s, 3 H, CH3Ar), 2.46-2.40 (m,
2 H), 2.23-2.14 (m, 1 H), 2.00-1.92 (m, 1 H), 1.96 (s, 3
H, ArCH=CCH3), 1.64-1.56 (m, 2 H), 1.47 (dddd, J = 12.5,
12.5, 4.0, 4.0 Hz, 1 H), 1.40-1.00 (m, 2 H), 1.26 (s, 3 H,
C(CH3)2), 1.18 (d, J = 7.0 Hz, 3 H, CH3CH(C=O)), 1.06 (s,
3 H, C(CH3)2), 0.98 (d, J = 6.5 Hz, 3 H, CH3CHCH2); 13C
NMR (125.7 MHz, CDC13) d 219.9, 170.5, 161.0, 137.4,

136.8, 135.6, 134.5, 125.6, 116.1, 77.2, 76.1, 72.5, 52.3, 43.8, 38.8, 37.6, 36.1, 32.6, 30.3, 27.2, 21.5, 20.4, 16.6, 16.0, 15.1, 13.7; HRMS (FAB), calcd for $C_{26}H_{40}NO_6$ (M + H+) 462.2856, found 462.2866.

Synthesis of Hydroxy Lactones 173 and 174 as illustrated in Figure 27. Cyclization of Diene 165 via Olefin Metathesis. To a solution of diene 165 (1.0 equiv) in CH_2Cl_2 (0.0015 M) was added bis(tricyclohexylphosphine)benzylidine ruthenium dichloride ($RuCl_2(=CHPh)(PCy_3)_2$, 0.2 equiv) and the reaction mixture was allowed to stir at 25 °C for 20 h. After the completion of the reaction was established by TLC, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (silica gel, 20% EtOAc in hexanes) to give hydroxy lactones 173 (25%) and 174 (63%).

Synthesis of cis-Dihydroxy Lactone 175 as illustrated in Figure 27. Desilylation of Compound 173. Silyl ether 173 (1.0 equiv) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-CH_2Cl_2 (0.01 M) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h (completion of the reaction by TLC). The work-up procedure was completed by the addition of saturated aqueous NHCO3 solution, extraction with EtOAc and drying of the combined organic layers with MgSO4. Evaporation of the solvents followed by flash column

chromatography (silica gel, ether) resulted in pure cis-dihydroxy lactone **175** (75%).

Synthesis of trans-Dihydroxy Lactone 176 as illustrated in Figure 27; Desilylation of Compound 174. Silyl ether **174** (1.0 equiv) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-CH2Cl2 (0.01 M) at 0 °C. The reaction mixture was stirred at 0 °C for 8 h (completion of the reaction by TLC). The work-up procedure was completed by the addition of saturated aqueous NHCO3 solution, extraction with EtOAc and drying of the combined organic layers with MgSO4. Evaporation of the solvents followed by flash column chromatography (silica gel, ether) resulted in pure trans-dihydroxy ester **9** (72%).

Synthesis of Epoxalones 161 and 170 as illustrated in Figure 26; Epoxidation of cis-Hydroxy Lactone 168. To a solution of **168** (1.0 equiv) in acetonitrile (0.05 M) was added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na2EDTA, 1.0 equiv) and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (1.0 equiv) was added, followed by a portionwise addition of Oxone® (10.0 equiv) and NaHCO3 (16.0 equiv) with stirring, until the disappearance of starting material was detected by TLC. The reaction mixture was then treated with excess dimethyl sulfide and immediately purified by flash column chromatography (silica gel, ether). Further purification by preparative

thin layer chromatography (250 mm silica gel plate, ether) provided epoxide 161 (34%) and a-isomeric epoxide 5 (15%). 161 : Rf = 0.23 (silica gel, Ether); [α]D = -25.2 (c 0.31, CHCl3); IR (film) nmax 3417, 2927, 2866, 1731, 1692, 1584, 1260, 756 cm-1; 1H-NMR (500 MHz, CDCl3) d = 7.50 (s, 1 H, ArH), 6.35 (s, 1 H, ArCH=CCH3), 5.44 (dd, 1 H, J = 8.0, 2.5 Hz, CO2CH), 4.12 (dd, 1 H, J = 10.0, 3.0 Hz, (CH3)2CCH(OH), 3.81 (dd, J = 5.0, 4.0 Hz, 1 H, CHOH(CHCH3)), 3.66 (bs, 1 H, OH), 3.23 (qd, J = 7.0, 5.5 Hz, 1 H, CH3CH(C=O)), 3.02 (ddd, J = 7.0, 4.5, 4.5 Hz, 1 H, CH2CH-O(epoxide)CH), 2.90 (ddd, J = 7.5, 4.0, 4.0 Hz, 1 H, CH2CH-O(epoxide)CH), 2.54 (dd, J = 14.5, 10.0 Hz, 1 H, CH2COO), 2.46 (s, 3 H, CH3Ar), 2.45 (dd, J = 14.5, 3.0 Hz, 1 H, CH2COO), 2.08 (ddd, J = 15.0, 5.0, 3.0 Hz, 1 H, CH2CH-O(epoxide)CH), 2.01 (s, 3 H, ArCH=CCH3), 1.88 (ddd, J = 15.5, 7.5, 7.5 Hz, 1 H, CH2CH-O(epoxide)CH), 1.78-1.72 (m, 1 H), 1.72-1.65 (m, 1 H), 1.40-1.15 (m, 5 H), 1.36 (s, 3 H, C(CH3)2), 1.17 (d, 3 H, J = 7.0 Hz, CH3CH(C=O)), 1.11 (s, 3 H, C(CH3)2), 1.00 (d, J = 6.9 Hz, 3 H, CH3CHCH2); 13C NMR (125.7 MHz, CDCl3) d 220.1, 170.5, 161.0, 137.2, 136.7, 135.9, 116.3, 76.3, 74.9, 73.8, 57.4, 54.3, 52.6, 43.8, 38.7, 36.1, 31.3, 30.4, 26.9, 23.8, 21.4, 21.1, 17.2, 15.8, 14.4, 13.8; HRMS (FAB), calcd for C26H40NO7 (M + H+) 478.2805, found 478.2790.

Synthesis of Epoxalones 171 and 172 as illustrated in Figure 26; Epoxidation of trans-Hydroxy Lactone 169. To a solution of 169 (1.0 equiv) in acetonitrile (0.05 M) was added a 0.0004 M aqueous

solution of disodium salt of ethylenediaminetetraacetic
acid (Na2EDTA, 1.0 equiv) and the reaction mixture was
cooled to 0 oC. 1,1,1-Trifluoroacetone (1.0 equiv) was
added, followed by a portionwise addition of Oxone® (10.0
5   equiv) and NaHCO3 (16.0 equiv) with stirring, until the
disappearance of starting material was detected by TLC.
The reaction mixture was then treated with excess dimethyl
sulfide and immediately purified by flash column
chromatography (silica gel, ether). Further purification
10   by preparative thin layer chromatography (250 mm silica
gel plate, ether) provided epoxide 171 (25%) and α-
isomeric epoxide 172 (20%).

**Synthesis of Epoxalones 177 and 178 as illustrated
15   in Figure 27; Epoxidation of cis-Hydroxy Lactone
175.** To a solution of 175 (1.0 equiv) in acetonitrile
(0.05 M) was added a 0.0004 M aqueous solution of disodium
salt of ethylenediaminetetraacetic acid (Na2EDTA, 1.0
equiv) and the reaction mixture was cooled to 0 °C. 1,1,1-
20   Trifluoroacetone (1.0 equiv) was added, followed by a
portionwise addition of Oxone® (10.0 equiv) and NaHCO3
(16.0 equiv) with stirring, until the disappearance of
starting material was detected by TLC. The reaction
mixture was then treated with excess dimethyl sulfide and
25   immediately purified by flash column chromatography
(silica gel, ether). Further purification by preparative
thin layer chromatography (250 mm silica gel plate, ether)
provided epoxide 177 (38%) and α-isomeric epoxide 178
(17%).

**Synthesis of Epoxalones 179 and 180 as illustrated
in Figure 27; Epoxidation of trans-Hydroxy
Lactone 176.** To a solution of 176 (1.0 equiv) in
acetonitrile (0.05 M) was added a 0.0004 M aqueous
solution of disodium salt of ethylenediaminetetraacetic
acid (Na2EDTA, 1.0 equiv) and the reaction mixture was
cooled to 0 oC. 1,1,1-Trifluoroacetone (1.0 equiv) was
added, followed by a portionwise addition of Oxone® (10.0
equiv) and NaHCO3 (16.0 equiv) with stirring, until the
disappearance of starting material was detected by TLC.
The reaction mixture was then treated with excess dimethyl
sulfide and immediately purified by flash column
chromatography (silica gel, ether). Further purification
by preparative thin layer chromatography (250 mm silica
gel plate, ether) provided epoxide 179 (22%) and α-
isomeric epoxide 180 (13%).

**Synthesis of cis-Bis(TBS) Ether 183 as illustrated in
Figure 29** A solution of alcohol 181 (148 mg, 0.32 mmol) and
2,6-lutidine (560 ml, 4.8 mmol, 15 equiv) in CH₂Cl₂ (3.2 mL,
0.1 M), at 0 °C, is treated with tert-butyldimethylsilyl
trifluoromethanesulfonate (TBSOTf, 735 mL, 3.2 mmol, 10
equiv) and stirred at this temperature for 30 minutes,
whereupon no starting material is detected by TLC. The
reaction mixture is quenched by pouring it into saturated
aqueous NH₄Cl (10 mL). Extractions with ether (2 x 10 mL),
drying (MgSO₄) and concentration is followed by flash

chromatographic purification (silica gel, 7% EtOAc in hexanes) to provide bis(TBS)ether 183 (182 mg, 99%).

Synthesis of trans-Bis(TBS) Ether 184 as illustrated in Figure 29. Silylation of Alcohol 182. In accordance with the procedure describing the silylation of alcohol 181, a solution of alcohol 182 (77 mg, 0.17 mmol) and 2,6-lutidine (300 ml, 2.6 mmol, 15 equiv) in CH2Cl2 (1.7 mL, 0.1 M), at 0 °C, is treated with tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf, 390 mL, 1.7 mmol, 10 equiv) to provide bis(TBS)ether 183 (92 mg, 97%).

Synthesis of cis-Alcohol 185 as illustrated in Figure 29. A solution of TBS ether 183 (182 mg, 0.31 mmol) in MeOH (3.1 mL, 0.1 M) is treated with 10-camphorsulfonic acid (CSA, 72 mg, 0.31 mmol, 1.0 equiv) at room temperature for 12 h, until TLC indicates the disappearance of starting material. The mixture is then poured into into saturated aqueous NaHCO3 (10 mL), extracted with ether (3 x 10 mL) and dried (MgSO4). Flash column chromatography (silica gel, 20% EtOAc in hexanes) yields pure 185 (98 mg, 67%).

Synthesis of trans-Alcohol 186 as illustrated in Figure 29. In accordance with the procedure describing the desilylation of TPS ether 183, a solution of TPS ether 184 (31 mg, 0.05 mmol) in methanol (1.6 mL, 0.1 M) was treated with 10-camphorsulfonic acid (CSA, 37 mg, 0.16 mmol, 1.0 equiv) to yield diol 186 (51 mg, 69%) as a crystalline solid.

Synthesis of Carboxylic acid 187 as illustrated in Figure 29 Ethyl bromopyruvate (1.66 mL, 13.2 mmol, 1 equiv) and thioacetamide (1.05 g, 13.9 mmol, 1.05 equiv) are dissolved in 95% aqueous ethanol (14 mL, 1 M) and heated at reflux for 5 minutes. Completion of the reaction is indicated by TLC. The reaction mixture is then cooled to room temperature, concentrated in vacuo, suspended in CHCl3 (20 mL) and washed with saturated aqueous NaHCO3 (2 x 20 mL) and with H2O (20 mL). Drying (MgSO4) and concentration is followed by flash chromatographic purification (silica gel, EtOAc) to yield the corresponding ethyl ester of acid 7 (2.26 g, 100%). This ester is dissolved in THF-H2O (1:1; 14 mL, 1 M) and submitted to the action of lithium hydroxide (1.66 g, 39.6 mmol, 3.0 equiv). After stirring at room temperature for 45 min TLC indicates the disappearance of starting material. The mixture is poured into H2O (20 mL) and extracted with ether (2 x 20 mL). Acidification to pH ~ 2 to 3 with aqueous 4 N HCl is followed by extractions with EtOAc (6 x 20 mL). Drying (MgSO4) and concentration gives pure carboxylic acid 187 (1.36 g, 72%).

Synthesis of cis-Keto Ester 188 as illustrated in Figure 29. EDC Coupling of Alcohol 185 with Thiazole Acid 187. A suspension of thiazole acid 187 (54 mg, 0.38 mmol, 2.0 equiv), 4-(dimethylamino)pyridine (4-DMAP, 2.3 mg, 0.019 mmol, 0.1 equiv) and alcohol 185 (88 mg, 0.19 mmol, 1.0 equiv) in CH2Cl2 (3.8 mL, 0.05 M) is cooled to 0 oC and then treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 109 mg, 0.57 mmol, 3.0 equiv). The

reaction mixture is stirred at 0 °C for 2 h and then at 25 °C for 12 h, until TLC indicates completion of the reaction. The solution is separated between EtOAc (10 mL) and water (10 mL). The aqueous layer is extracted with EtOAc (2 x 10 mL) and dried (MgSO4). Evaporation of the solvents is followed by flash column chromatography (silica gel, 30% EtOAc in hexanes) results in pure keto ester 188 (102 mg, 92%).

Synthesis of trans-Keto Ester 189 as illustrated in Figure 29. By analogy to the procedure described above for the synthesis of keto ester 188, a solution of thiazole acid 187 (28 mg, 0.198 mmol, 2.0 equiv), 4-dimethylaminopyridine (4-DMAP, 1.2 mg, 0.0099 mmol, 0.1 equiv), and alcohol 186 (46 mg, 0.099 mmol, 1.0 equiv) in CH2Cl2 (2.0 mL) is treated with 1-ethyl-(3-dimethylaminopropyl)-3-carbodiimide hydrochloride (EDC, 57 mg, 0.297 mmol, 3.0 equiv) to provide, after flash column chromatography (silica gel, 20% EtOAc in hexanes), keto ester 189 (49 mg, 84%).

Synthesis of cis-Hydroxy Lactone 190 as illustrated in Figure 29. Silyl ether 188 (95 mg, 0.16 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid-CH2Cl2 (16 mL, 0.01 M) at 0 oC. The reaction mixture was stirred at 0 °C for 45 min (completion of the reaction by TLC), and then poured into sturated aqueous NaHCO3 (50 mL), extracted with EtOAc (3 x 20 mL), dried over MgSO4 and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (silica

gel, 50% EtOAc in hexanes) to obtain cis-hydroxy lactone 190 (74 mg, 96%).

Synthesis of trans-Dihydroxy Lactone 191 as illustrated in Figure 29. Silyl ether 189 (44 mg, 0.074 mmol) was treated with a freshly prepared solution of 20% (v/v) trifluoroacetic acid (TFA)-CH2Cl2 (7.4 mL, 0.01 M), according to the procedure described for cis-dihydroxy lactone 8, to yield, after flash column chromatography (silica gel, 50% EtOAc in hexanes), trans-dihydroxy ester 191 (33 mg, 93%)

Synthesis of Eposterones 192 and 194 as illustrated in Figure 29. To a solution of cis-hydroxy lactone 190 (19 mg, 0.039 mmol) in acetonitrile (390 mL, 0.1 M) is added a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na2EDTA, 200 mL, 0.2 M) and the reaction mixture is cooled to 0 oC. Excess of 1,1,1-trifluoroacetone (80 mL, 0.5 M) is added, followed by a portionwise addition of Oxone® (120 mg, 0.20 mmol, 5.0 equiv) and NaHCO3 (26 mg, 0.31 mmol, 8.0 equiv) with stirring, until the disappearance of starting material is detected by TLC. The reaction mixture is then directly passed through silica gel and eluted with 50% EtOAc in hexanes. Purification by preparative thin layer chromatography (250 mm silica gel plate, 70% EtOAc in hexanes) provides the diastereomeric eposterones 192 (9.5 mg, 48%) and 194 (3.4 mg, 17%).

Synthesis of Eposterones 193 and 195 as illustrated in Figure 29. As described for the epoxidation of cis-hydroxy lactone 190, trans-hydroxy lactone 191 (22 mg, 0.046 mmol) in MeCN (460 mL, 0.1 M) was treated with a 0.0004 M aqueous solution of disodium salt of ethylenediaminetetraacetic acid (Na2EDTA, 230 mL, 0.2 M), 1,1,1-trifluoroacetone (92 mL, 0.5 M), Oxone® (141 mg, 0.23 mmol, 5.0 equiv) and NaHCO3 (31 mg, 0.37 mmol, 8.0 equiv), to yield, after purification by preparative thin layer chromatography (250 mm silica gel plate, ether), eposterones 193 (7.3 mg, 32%) and 195 (5.2 mg, 23%).

Synthesis of Eposterones 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209 and 210 as illustrated in Figure 30. By simple modification of the esterification step, i.e. replacing the thiazole carboxylic acid 187 in Figure 29 with the known carboxylic acids found in epoxalone (198), eleutherobin (197) and taxol (196), other members of the eposterone family can be created including the various isomers: 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209 and 210.

Aldehyde 212. Reduction of Ester 211 as illustrated in Figure 31. Ethyl ester 211 (52.5 g, 0.306 mol) was dissolved in CH₂Cl₂ (1 L, 0.3 M) and cooled to -78 °C. DIBAL (490.0 mL, 1 M solution in CH₂Cl₂, 0.4896 mol, 1.6 equiv) was added dropwise via a cannula while the temperature of the reaction mixture was maintained at -78 °C. After the addition was complete, the reaction mixture was stirred at the same

temperature until its completion was verified by TLC (ca 1 h). Methanol (100 mL) was added at -78 °C and was followed by addition of EtOAc (1 L) and saturated aqueous NH₄Cl solution (300 mL). The quenched reaction mixture was allowed to warm

5 up to room temperature and stirred for 12 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, 10 ⟶ 90% ether in

10 hexanes) furnished the desired aldehyde **212** (33.6 g, 90%):

Synthesis of Aldehyde 213 as illustrated in Figure 31. Aromatic aldehyde **212** (31.1 g, 0.245 mol) was dissolved in benzene (500 mL) and 2-(triphenylphosphoranilidene)-

15 propionaldehyde (90.0 g, 0.282 mol, 1.15 equiv) was added. The reaction mixture was heated at reflux until the reaction was complete as judged by TLC (ca 2 h). Evaporation of the solvent under reduced pressure, followed by flash column chromatography (10 ⟶ 90% ether in hexanes) produced the

20 desired aldehyde **213** (40.08 g, 98%):

Synthesis of Alcohol 214. Allylboration of Aldehyde 213 as illustrated in Figure 31. Aldehyde **213** (20.0 g, 0.120 mol) was dissolved in anhydrous ether (400 mL) and the

25 solution was cooled to -100 oC. (+)-Diisopinocampheylallyl borane (1.5 equiv in pentane, prepared from 60.0 g of (-)-Ipc2BOMe and 1.0 equiv of allyl magnesium bromide according to the method described for the synthesis the corresponding thiazole), was added dropwise under vigorous stirring, and

the reaction mixture was allowed to stir for 1 h at the same temperature. Methanol (40 mL) was added at -100 oC, and the reaction mixture was allowed to warm up to room temperature. Amino ethanol (72.43 mL, 1.2 mol, 10.0 equiv) was added and 5 stirring was continued for 15 h. The work-up procedure was completed by the addition of saturated aqueous NH4Cl solution (200 mL), extraction with EtOAc (4 x 100 mL) and drying of the combined organic layers with MgSO4. Filtration, followed by evaporation of the solvents under reduced pressure and 10 flash column chromatography (silica gel, 35% ether in hexanes for several fractions until all the boron complexes were removed; then 70% ether in hexanes) provided alcohol 214 (24.09 g, 96%):

15 **Synthesis of Compound 5. Silylation of Alcohol 214 as illustrated in Figure 31.** Alcohol 214 (7.0 g, 0.033 mol) was dissolved in DMF (35 mL, 1.0 M), the solution was cooled to 0 ˚C and imidazole (3.5 g, 0.050 mol, 1.5 equiv) was added. After stirring for 5 min, tert-butyldimethylsilyl 20 chloride (6.02 g, 0.040 mol, 1.2 equiv) was added portionwise and the reaction mixture was allowed to stir at 0 ˚C for 45 min, and then at 25 ˚C for 2.5 h, after which time no starting alcohol was detected by TLC. Methanol (2 mL) was added at 0 oC and the solvent was removed under reduced 25 pressure. Ether (100 mL) was added, followed by saturated aqueous NH4Cl solution (20 mL), the organic phase was separated and the aqueous phase was extracted with ether (2 x 20 mL). The combined organic solution was dried (MgSO4), filtered over celite and the solvents were removed under

reduced pressure. Flash column chromatography (silica gel, 10 & 20% ether in hexanes) provided pure 215 (10.8 g, 99%).

Synthesis of Aldehyde 217 as illustrated in Figure 31.. Dihydroxylation of Olefin 215 and 1,2 Glycol Cleavage of diol 216. Olefin 215 (16.7 g, 51.6 mmol) was dissolved in THF/tBuOH (1 : 1, 500 mL) and H_2O (50 mL). 4-Methylmorpholine N-oxide (NMO) (7.3 g, 61.9 mmol, 1.2 equiv) was added at 0 °C, followed by OsO_4 (5.2 mL, solution in tBuOH 1.0 mol%, 2.5% by weight). The mixture was vigorously stirred for 2.5 h at 0 °C and then for 12 h at 25 °C. After completion of the reaction, Na_2SO_3 (5.0 g) was added at 0 °C, followed by H_2O (100 mL). Stirring was continued for another 30 min and then ether (1 L) was added, followed by saturated aqueous NaCl solution (2 x 100 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. Flash column chromatography (silica gel, ether & EtOAc) provided 17.54 g (95%) of the expected 1,2-diol 216 as a 1:1 mixture of diastereoisomers:

The diol obtained from 215 as described above (5.2 g, 14.5 mmol) was dissolved in EtOAc (150 mL) and cooled to 0 °C. $Pb(OAc)_4$ (8.1 g, 95% purity, 18.3 mmol, 1.2 equiv) was then added portionwise over 10 min, and the mixture was vigorously stirred for 15 min at 0 °C. After completion of the reaction, the mixture was filtered through silica gel and washed with 60% ether in hexanes. The solvents were then

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removed under reduced pressure providing pure aldehyde 217 (4.7 g, 98%):

Synthesis of Alcohol 218 as illustrated in Figure 31.
Reduction of Aldehyde 217. A solution of aldehyde 215 (440 mg, 1.35 mmol) in MeOH (13 mL) was treated with NaBH4 (74 mg, 2.0 mmol, 1.5 equiv) at 0 °C for 15 min. The solution was diluted with ether (100 mL) and then saturated aqueous NH4Cl solution (5 mL) was carefully added. The organic phase was washed with brine (10 mL), dried (MgSO4) and concentrated. Flash column chromatography (silica gel, 60% ether in hexanes) gave alcohol 218 (425 mg, 96%) as a colorless oil.

Synthesis of Iodide 219 as illustrated in Figure 31.
Iodination of Alcohol 218. A solution of alcohol 218 (14.0 g, 42.7 mmol) in ether: MeCN (3:1, 250 mL) was cooled to 0 °C. Imidazole (8.7 g, 128.1 mmol, 3.0 equiv), Ph3P (16.8 g, 64.1 mmol, 1.5 equiv), and iodine (16.3 g, 64.1 mmol, 1.5 equiv) were sequentially added and the mixture was stirred for 0.5 h at 0 °C. A saturated aqueous solution of Na2S2O3 (50 mL) was added, followed by the addition of ether (600 mL). The organic phase was washed with brine (50 mL), dried (MgSO4), and the solvents were removed under vacuum. Flash column chromatography (silica gel, 15% ether in hexanes) gave pure iodide 219 (16.6 g, 89%) as a colorless oil:

Synthesis of Phosphonium Salt 220 as illustrated in Figure 31. A mixture of iodide 219 (16.5g, 37.7 mmol) and Ph3P (10.9 g, 41.5 mmol, 1.1 equiv) was heated neat at 100 °C

for 2 h. Purification by flash column chromatography (silica gel, CH2Cl2; then 7% MeOH in CH2Cl2) provided phosphonium salt 220 (25.9 g, 98%) as a white solid.

5   **Synthesis of Olefinic Compound 222 as illustrated in Figure 32.** Phosphonium salt 220 (9.0 g, 12.93 mmol, 1.5 equiv) was dissolved in THF (90 mL) and the solution was cooled to 0 °C. Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF, 12.84 mL, 12.84 mmol, 1.48 equiv) was
10   slowly added and the resulting mixture was stirred at 0 °C for 15 min. The reaction mixture was then cooled to -20 °C before ketone 221 (2.23 g, 8.62 mmol, 1.0 equiv) in THF (10 mL) was added and the reaction mixture was stirred at the same temperature for 12 h. Saturated aqueous NH4Cl solution
15   (50 mL) was added and the mixture was extracted with ether (200 mL). The organic phase was washed with brine (2 x 100 mL), dried (MgSO4) and concentrated to afford, after flash column chromatography (silica gel, 2% ether in hexanes) olefins 222 (3.8g, 73%, Z:E ca. 1:1 by 1H NMR).

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Synthesis of Hydroxy Olefins 223 as illustrated in Figure 32. Desilylation of Silylether 222. Silylether 222 (3.80 g, 6.88 mmol) was dissolved in CH2Cl2 : MeOH (1:1, 70 mL) and the solution was cooled to 0 °C prior to addition of
25   CSA (1.68 g, 7.23 mmol, 1.05 equiv) during a 5 min period. The resulting mixture was stirred for 30 min at 0 °C, and then for 1 h at 25 °C. Et3N (1.57 mL, 7.23 mmol, 1.05 equiv) was added, and the solvents were removed under reduced

pressure. Flash column chromatography (silica gel, 50% ether in hexanes) furnished pure hydroxy compound 223 (2.9 g, 97%).

Synthesis of Aldehyde 224 as illustrated in Figure 32

5 Oxidation of Alcohol 223. Alcohol 223 (mixtures of Z and E geometrical isomers, 4.60 g, 10.64 mmol) was dissolved in CH2C12 (105 mL, 0.1 M). DMSO (35 mL), Et3N (7.4 mL, 53.20 mmol, 5.0 equiv) and SO3•pyr (3.4 g, 21.28 mmol, 2.0 equiv) were added at 25 °C and the resulting mixture was stirred for
10 30 min. Saturated aqueous NH4Cl solution (50 mL) and ether (300 mL) were added, and the organic phase was separated and washed with brine (2 x 30 mL), dried (MgSO4), and concentrated under reduced pressure. Flash column chromatography (silica gel, 20% ether in hexanes) furnished
15 aldehyde 224 (4.40 g, mixture of Z:E isomers, ca 1:1, 95%).

Synthesis of tris(Silylethers) 226 and 227 as illustrated in Figure 32. Aldol Reaction of Keto Acid 225 with Aldehyde 224. A solution of keto acid 225 (1.52 g, 5.10
20 mmol, 1.2 equiv) in THF (10 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (1.78 mL, 12.78 mmol) was added to n-BuLi (7.95 mL, 1.6 M solution in hexanes, 12.78 mmol) in 20 mL of THF at 0 °C] at -78 °C. After stirring for 15 min, the solution was allowed to warm
25 to -40 °C, and after 0.5 h at that temperature it was recooled to -78 °C. A solution of aldehyde 224 (1.79 g, 4.24 mmol, 1.0 equiv) was added dropwise and the resulting mixture was stirred for 15 min, and then quenched at -78 °C by slow addition of saturated aqueous NH4Cl solution (20 mL). The

reaction mixture was warmed to 0 °C, and AcOH (2.03 mL, 26.84 mmol, 6.3 equiv) was added, followed by addition of EtOAc (50 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic solution was dried over $MgSO_4$ and concentrated under vacuum to afford a mixture of aldol products in a ca 1:1 ratio (1H NMR) and unreacted keto acid 225. The mixture was dissolved in CH_2Cl_2 (50 mL) and treated, at 0 °C, with 2,6-lutidine (3.2 mL, 27.36 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (4.2 mL, 18.24 mmol). After stirring for 2 h (complete reaction by TLC), aqueous HCl (20 mL, 10% solution) was added and the resulting biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic solution was washed with brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a mixture of the tetra-tert-butyldimethylsilyl ethers. The crude product was dissolved in MeOH (50 mL) and K_2CO_3 (1.40 g, 10.20 mmol) was added at 25 °C. The reaction mixture was vigorously stirred for 15 min, and then filtered. The residue was washed with MeOH (20 mL) and the solution was acidified with ion exchange resin (DOWEX 50WX8-200) to pH 4-5, and filtered again. The solvent was removed under reduced pressure and the resulting residue was dissolved in EtOAc (50 mL) and washed with saturated aqueous NH_4Cl solution (50 mL). The aqueous phase was extracted with EtOAc (4 x 25 mL) and the combined organic solution was dried ($MgSO_4$), filtered and concentrated to furnish a mixture of carboxylic acids 226, 227 and 225 Purification by preparative thin layer chromatography (silica

gel, 5% MeOH in CH2Cl2), gave pure acids226 (1.1 g, 31% from 224) and 227 (1.0 g, 30% from 224) as colorless oils.

**Synthesis of Hydroxy Acid 228 as illustrated in Figure
32.** Selective Desilylation of 226. A solution of tris(silyl) ether 226 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO4) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH2Cl2) to provide hydroxy acid 228 (203 mg, 78%) as a yellow oil.

**Synthesis of Lactones 230 and 229 as illustrated in
Figure 33.** A solution of hydroxy acid 228 (140 mg, mixture of Z and E isomers, ca 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 °C with Et3N (58 mL, 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 mL, 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by preparative thin layer chromatography (silica gel, 5% MeOH in CH2Cl2), gave pure

lactones 230 (50 mg, 37%) and 229 (54 mg, 40%) as colorless oils.

Synthesis of Dihydroxy lactone 232 as illustrated in Figure 33. To lactone 230 (50 mg, 0.071 mmol), cooled to -20 ℃, was added a freshly prepared 20% (v/v) CF3COOH solution in CH2C12 (400 mL). The reaction mixture was allowed to reach 0 ℃ and was stirred for 1 h at that temperature. The solvents were evaporated under reduced pressure and the crude product was purified by preparative thin layer chromatography (silica gel, 6% MeOH in CH2C12) to afford pure dihydroxy lactone 232 (31 mg, 92%).

Synthesis of Dihydroxy Lactone 231 as illustrated in Figure 33. Dihydroxy lactone 231 was prepared from bis(silylether) lactone 229 (40.0 mg, 0.055 mmol) by treatment with CF3COOH according to the same procedure described above for the preparation of 232. Obtained pure 231 (24.3 mg, 89%).

Synthesis of Compound 235 and its a-epoxide epimer 236 as illustrated in Figure 33. Procedure A: To a solution of lactone 232 (3.0 mg, 6.1 mmol) in benzene (0.2 mL) at -10 ℃ was added meta-chloroperbenzoic acid (2.9 mg, 50-60% purity, 8.4-10.1 mmol, 1.4-1.6 equiv) and the reaction mixture was stirred at that temperature for 2 h at which time TLC indicated completion of the reaction. The reaction mixture was diluted with EtOAc (5 mL), washed with saturated aqueous NaHCO3 solution (2 mL), and the aqueous phase was

extracted with EtOAc (3 x 2 mL). The combined organic layer was dried (MgSO4), filtered and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in CH2Cl2) provided a mixture of 235 and its a-epoxy diastereoisomer 236 (2.0 mg, 66%, ca 5:1 ratio by 1H NMR), which was separated to its components by a second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnishing pure 235 (1.6 mg, 52%) as a white solid. Procedure B: To a solution of lactone 232 (5.0 mg, 10.2 mmol) in CH2Cl2 (0.5 mL) at -50 °C was added dropwise a solution of dimethyldioxirane in acetone untill the starting material disappeared (TLC). The resulting solution was concentrated, and the crude product was subjected to preparative thin layer chromatography (silica gel, 5% MeOH in CH2Cl2) to give 235 and its a-epoxy diastereoisomer 236 in ca 5:1 ratio (3.9 mg, 75%). Pure 235 was obtained (3.1 mg, 60%) by preparative thin layer chromatography as described above. Procedure C: To a solution of 232 (10 mg, 21.0 mmol) in MeCN (200 mL) was added 4.10-4 M aqueous solution of disodium ethylenediaminetetraacetate (Na2EDTA, 120 mL) and the reaction mixture was cooled to 0 °C. 1,1,1-Trifluoroacetone (200 mL) was added followed by a mixture of Oxone® (61 mg, 0.10 mmol, 5.0 equiv) and NaHCO3 (14.0 mg, 0.17 mmol, 8.0 equiv) with stirring until completion of the reaction was revealed by TLC. The reaction mixture was treated with excess Me2S (100 mL) and water (500 mL) and was then extracted with EtOAc (4 x 2 mL). The combined organic phase was dried (MgSO4), filtered, and concentrated. Purification by preparative thin layer chromatography (silica gel, 5% MeOH in

CH2C12) gave a mixture of 235 and its a-epoxide epimer 236 (8.6 mg, 78% total yield). A second preparative thin layer chromatography (silica gel, 70% EtOAc in hexanes) furnished pure 235 (6.4 mg, 65%) as a white solid.

Synthesis of Epothilone 23 and 24 as illustrated in Figure 33. Procedure A: Compound 231 (5.0 mg, 10.2 mmol) was epoxidised with mCPBA according to procedure A described above for 232 to yield a mixture of 234 and its a-epoxy-diastereoisomer 233 (3.7 mg, 73% total yield, ca 4:1 by 1H NMR). Procedure B: The epoxidation of 231 (3.0 mg, 6.1 mmol) according to the procedure described above for 232 led to epothilones 233 and its a-epoxy diastereoisomer 234 (2.6 mg, 86% total yield, ca 1:1 ratio by 1H NMR).

Synthesis of α,β-Unsaturated Ester 237 as illustrated in Figure 34. A mixture of aldehyde 217 (5.17 g, 15.9 mmol) and stabilized ylide (8.92 g, 24.0 mmol, 1.5 equiv, prepared from 4-bromo-1-butene by: (i) phosphonium salt formation; (ii) anion formation with NaHMDS; and (iii) quenching with MeOC(O)Cl)29) in benzene (300 mL, 0.05 M) was heated at reflux for 3 h. After cooling to 25 °C, the solvent was removed under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 30% ether in hexanes) to afford a,b-unsaturated ester 237 (7.15 g, 95%).

Synthesis of Allylic Alcohol 238 as illustrated in Figure 34. Methyl ester 237 (6.1 g, 14.4 mmol) was dissolved in THF (80 mL) and cooled to -78 °C. DIBAL (44.0

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mL, 1 M solution in CH2Cl2, 44.0 mmol, 3.0 equiv) was added dropwise at -78 oC, and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with MeOH (1.0 mL) at -78 °C, and then ether (100 mL) was added, followed by saturated aqueous sodium-potasium tartrate solution (10 mL). The resulting mixture was allowed to warm up to room temperature, where it was stirred for 3 h. The organic layer was separated and the aqueous phase was extracted with ether (2 x 50 mL). The combined organic phase was dried (MgSO4), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 40 to 80% ether in hexanes) furnished alcohol 238 (5.58 g, 98%).

Synthesis of Compound 239 as illustrated in Figure 34. Chlorination of Alcohol 238. Alcohol 238 (3.00 g, 7.60 mmol) was dissolved in CCl4 (75 mL, 0.1 M) and Ph3P (4.00 g, 15.2 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature and the solvent was removed under reduced pressure. Flash column chromatography (silica gel, 10% ether in hexanes) furnished pure 239 (2.6 g, 83%).

Synthesis of Compound 240 as illustrated in Figure 34. Reduction of 239. Compound 239 (2.60 g, 6.30 mmol) was dissolved in THF (60 mL, 0.1 M) and cooled to 0 °C. LiEt3BH (12.6 ml, 1.0 M solution in THF, 12.6 mmol, 2.0 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. Aqueous NaOH (1.0 mL, 3.0 N) solution was added followed by addition of Et2O (150 mL). The organic phase was

washed with brine (2 x 20 mL), dried (MgSO4) and concentrated. Flash column chromatography (silica gel, 20% ether in hexanes) furnished pure 240 (2.38 g, 99%).

5   **Synthesis of Primary Alcohol 241 as illustrated in Figure 34.** Selective Hydroboration of Olefinic Compound 240. Compound 240 (1.1 g, 2.91 mmol) was dissolved in THF (3.0 mL, 1.0 M) and the solution was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M solution in THF, 3.5 mmol, 1.2 equiv) was

10   added, and the reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH (7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with stirring, followed by H2O2 (2.4 mL, 30%, aqueous solution). Stirring was continued for 0.5 h at 0 °C, after which time the reaction mixture was diluted with ether (30

15   mL). The organic solution was separated and the aqueous phase was extracted with ether (2 x 15 mL). The combined organic layer was washed with brine (2 x 5 mL), dried (Na2SO4) and concentrated in vacuo. Flash column chromatography (silica gel, 50 & 80% ether in hexanes)

20   furnished primary alcohol 241 (1.0 g, 91%).

Synthesis of Iodide 242 as illustrated in Figure 34. Iodide 242 (1.18 g, 92%) was prepared from alcohol 241 (1.0 g, 2.53 mmol) according to the procedure described above for

25   219.

Synthesis of Hydrazone 243 as illustrated in Figure 34. Alkylation of SAMP Hydrazone with Iodide 242. SAMP hydrazone (337 mg, 0.2 mmol, 2.0 equiv) in THF (2.5 mL), was

added to a freshly prepared solution of LDA at 0 °C [diisopropylamine (277 mL, 0.20 mmol, 2.0 equiv) was added to n-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol. 2.0 equiv) in 2.5 mL of THF at 0 °C] at 0°C. After stirring at

5 that temperature for 8 h, the resulting yellow solution was cooled to -100 °C, and a solution of iodide 242 (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to -20 °C over 10 h, and then poured into saturated aqueous NH4Cl

10 solution (5 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were dried (MgSO4), filtered and evaporated. Purification by flash column chromatography on silica gel (20 & 40% ether in hexanes) provided hydrazone 243 (380 mg, 70%, de > 98% by 1H NMR) as a yellow oil.

15

Synthesis of Nitrile 244 as illustrated in Figure 35. Monoperoxyphthalic acid magnesium salt (MMPP•6H2O, 233 mg, 0.38 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0

20 °C. Hydrazone 243 (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 °C until the reaction was complete by TLC (ca 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous NaHCO3 solution (5

25 mL). The organic layer was separated and the aqueous phase was extracted with ether (10 mL). The combined organic solution was washed with water (5 mL) and brine (5 mL), dried (MgSO4) and concentrated. Flash column chromatography

(silica gel, 50% ether in hexanes) afforded nitrile 244 (53 mg, 80%) as a colorless oil.

Synthesis of Aldehyde 224 as illustrated in Figure 35.
5 Nitrile 244 (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to -78 °C. DIBAL (245 mL, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at -78 oC and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca 1 h). Methanol
10 (150 mL) and aqueous HCl (150 mL, 1 N solution) were sequentially added and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 5
15 mL) and the combined organic solution was washed with brine (5 mL), dried (MgSO4), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 15% ether in hexanes) furnished pure aldehyde 224 (44 mg, 82%):

20 **Synthesis of tris(Silylether) 245 as illustrated in Figure 35.** Aldol Reaction of Ketone with Aldehyde 224. A solution of ketone (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (94 mL, 0.67 mmol) was added to n-BuLi (
25 0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0 °C] in THF (2.5 mL) at -78 °C. After stirring for 15 min at -78 °C, the solution was allowed to warm to -40 °C over a period of 1 h. The reaction mixture was cooled to -78 °C, and a solution of aldehyde 224 (244 mg, 0.56 mmol, 1.0

equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78 °C, and then quenched by dropwise addition of saturated aqueous NH4Cl solution (2 mL). The aqueous phase was extracted with ether (3 x 5 mL)

5 and the combined organic layer was dried (MgSO4) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products (354 mg (85%) of ca 3:1 by 1H NMR). Separation of these diastereoisomers was carried out by

10 preparative thin layer chromatography (silica gel, 20% ether in hexanes) leading to pure 245 (270 mg, 64%).

Synthesis of tetra(Silylether) 246 as illustrated in Figure 35. Compound 245 (275 mg, 0.33 mmol) was dissolved

15 in CH2Cl2 (5.0 mL), cooled to 0 °C and treated with 2,6-lutidine (76 mL, 0.66 mmol, 2.0 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (88 mL, 0.39 mmol, 1.2 equiv). After stirring for 2 h at 0 °C, the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N

20 solution) and the aqueous phase was extracted with CH2Cl2 (3 x 5 mL). The combined organic solution was washed with brine (5 mL), dried (MgSO4) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetra(silylether)

25 246 (300 mg, 96%) as a colorless oil.

Synthesis of Alcohol 247 as illustrated in Figure 35. Alcohol 247 (200 mg, 85%) was obtained from compound 246 (264

mg, 0.28 mmol) according to the procedure described above for 223.

Synthesis of Aldehyde 248 as illustrated in Figure 35. Oxidation of Alcohol 247. To a solution of oxalyl chloride (54 mL, 0.61 mmol, 2.0 equiv) in CH2C12 (5.0 mL) was added dropwise DMSO (86 mL, 1.21 mmol, 4.0 equiv) at -78 °C. After stirring for 15 min at -78 °C, a solution of alcohol 247 (255 mg, 0.305 mmol, 1.0 equiv) in CH2C12 (2.0 mL) was added dropwise at -78 °C over a period of 5 min. The solution was stirred at -78 °C for 30 min, and then Et3N (250 mL, 1.82 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm to 0 °C over a period of 30 min and then ether (20 mL) was added, followed by saturated aqueous NH4Cl solution (10 mL). The organic phase was separated and the aqueous phase was extracted with ether (2 x 10 mL). The combined organic solution was dried (MgSO4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided aldehyde 248 (241 mg, 95%) as a colorless oil.

Synthesis of Carboxylic Acid 249 as illustrated in Figure 35. Aldehyde 248 (224 mg, 0.29 mmol), tBuOH (5.0 mL), isobutylene (5.0 mL, 2 M solution in THF, 10.0 mmol), H2O (1.0 mL), NaClO2 (90 mg, 0.86 mmol, 3.0 equiv) and NaH2PO4 (60 mg, 0.43 mmol, 1.5 equiv) were combined and stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was

subjected to flash column chromatography (silica gel, 6% MeOH in CH2Cl2) to afford carboxylic acid 249 (220 mg, 90%).

Synthesis of Hydroxy Acid 250 as illustrated in Figure 35. A solution of tris(silyl) ether 249 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO4) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH2Cl2) to provide hydroxy acid 250 (203 mg, 78%) as a yellow oil:

Synthesis of Lactone 229 as illustrated in Figure 36. Macrolactonization of Hydroxy Acid 250. A solution of hydroxy acid 250 (140 mg, mixture of Z and E isomers, ca 1:1, 0.189 mmol) in THF (2.6 mL) was treated at 0 °C with Et3N (58 mL, 0.416 mmol, 2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (29.4 mL, 0.246 mmol, 1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (233 mg, 1.896 mmol, 10.0 equiv) in toluene (90 mL, 0.002 M) at 25 °C and stirred at that temperature for 10 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by preparative thin layer chromatography (silica gel, 5% MeOH in CH2Cl2), gave pure lactone 229 (104 mg, 77%).

Synthesis of Compound 252 as illustrated in Figure 37.
Compound 251, trityl chloride (2.0 eq.) and DMAP (1.1 eq.)
were dissolved in DMF (0.1 M) and the reaction mixture heated
5   at 60 °C for 12 h. The solvent was removed under reduced
pressure and flash column chromatography (silica gel, ether
in hexanes) furnished pure 252.

Synthesis of Primary Alcohol 253 as illustrated in
10   **Figure 37.**   Selective Hydroboration of Olefinic Compound
252. Compound 252 was cooled to 0 °C. 9-BBN (7.0 mL, 0.5 M
solution in THF, 3.5 mmol, 1.2 equiv) was added, and the
reaction mixture was stirred for 2 h at 0 °C. Aqueous NaOH
(7.0 mL, 3 N solution, 21.0 mmol, 7.2 equiv) was added with
15   stirring, followed by H2O2 (2.4 mL, 30%, aqueous solution).
Stirring was continued for 0.5 h at 0 °C, after which time
the reaction mixture was diluted with ether (30 mL).   The
organic solution was separated and the aqueous phase was
extracted with ether (2 x 15 mL). The combined organic layer
20   was washed with brine (2 x 5 mL), dried (Na2SO4) and
concentrated in vacuo. Flash column chromatography (silica
gel, 50 to 80% ether in hexanes) furnished primary alcohol
254 (1.0 g, 91%).

25   **Synthesis of Iodide 254 as illustrated in Figure 37.**
Iodide 254 (1.18 g, 92%) was prepared from alcohol 253 (1.0
g, 2.53 mmol) according to the procedure described above for
219.

Synthesis of Hydrazone 255 as illustrated in Figure 37. Alkylation of SAMP Hydrazone with Iodide 254. SAMP hydrazone (337 mg, 0.2 mmol, 2.0 equiv) in THF (2.5 mL), was added to a freshly prepared solution of LDA at 0 ˚C [diisopropylamine (277 mL, 0.20 mmol, 2.0 equiv) was added to n-BuLi (1.39 mL, 1.42 M solution in hexanes, 0.20 mmol. 2.0 equiv) in 2.5 mL of THF at 0 ˚C] at 0˚C. After stirring at that temperature for 8 h, the resulting yellow solution was cooled to -100 ˚C, and a solution of iodide 254 (0.5 g, 0.99 mmol, 1.0 equiv) in THF (3 mL) was added dropwise over a period of 5 min. The mixture was allowed to warm to -20 ˚C over 10 h, and then poured into saturated aqueous NH4Cl solution (5 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were dried (MgSO4), filtered and evaporated. Purification by flash column chromatography on silica gel (20 to 40% ether in hexanes) provided hydrazone 255 (380 mg, 70%, de > 98% by 1H NMR) as a yellow oil.

Synthesis of Nitrile 256 as illustrated in Figure 37. Monoperoxyphthalic acid magnesium salt (MMPP·6H2O, 233 mg, 0.38 mmol, 2.5 equiv) was suspended in a rapidly stirred mixture of MeOH and pH 7 phosphate buffer (1:1, 3.0 mL) at 0 ˚C. Hydrazone 255 (83 mg, 0.15 mmol, 1.0 equiv) in MeOH (1.0 mL) was added dropwise, and the mixture was stirred at 0 ˚C until the reaction was complete by TLC (ca 1 h). The resulting suspension was placed in a separating funnel along with ether (15 mL) and saturated aqueous NaHCO3 solution (5 mL). The organic layer was separated and the aqueous phase was extracted with ether (10 mL). The combined organic

solution was washed with water (5 mL) and brine (5 mL), dried (MgSO4) and concentrated. Flash column chromatography (silica gel, 50% ether in hexanes) afforded nitrile 256 (53 mg, 80%) as a colorless oil.

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Synthesis of Aldehyde 257 as illustrated in Figure 37.
Nitrile 256 (53 mg, 0.12 mmol) was dissolved in toluene (2.0 mL) and cooled to -78 °C. DIBAL (245 mL, 1 M solution in toluene, 0.22 mmol, 2.0 equiv) was added dropwise at -78 oC

10 and the reaction mixture was stirred at that temperature until its completion was verified by TLC (ca 1 h). Methanol (150 mL) and aqueous HCl (150 mL, 1 N solution) were sequentially added and the resulting mixture was brought up to 0 °C and stirred at that temperature for 30 min. Ether (5

15 mL) and water (2 mL) were added, and the organic layer was separated. The aqueous phase was extracted with ether (2 x 5 mL) and the combined organic solution was washed with brine (5 mL), dried (MgSO4), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel,

20 15% ether in hexanes) furnished pure aldehyde 257 (44 mg, 82%).

Synthesis of tris(Silylether) 258 as illustrated in Figure 38. Aldol Reaction of Ketone with Aldehyde 257. A

25 solution of ketone (270 mg, 0.67 mmol, 1.2 equiv) in THF (1.5 mL) was added dropwise to a freshly prepared solution of LDA [diisopropylamine (94 mL, 0.67 mmol) was added to n-BuLi (0.43 mL, 1.6 M solution in hexanes, 0.67 mmol) in 2.5 mL of THF at 0 °C] in THF (2.5 mL) at -78 °C. After stirring for

15 min at -78 °C, the solution was allowed to warm to -40 °C over a period of 1 h. The reaction mixture was cooled to -78 °C, and a solution of aldehyde 257 (244 mg, 0.56 mmol, 1.0 equiv) in THF (1.0 mL) was added dropwise. The resulting mixture was stirred for 15 min at -78 °C, and then quenched by dropwise addition of saturated aqueous NH4Cl solution (2 mL). The aqueous phase was extracted with ether (3 x 5 mL) and the combined organic layer was dried (MgSO4) and concentrated. Purification by flash column chromatography (silica gel, 20% ether in hexanes) provided a mixture of aldol products (354 mg (85%) of ca 3:1 by 1H NMR). Separation of these diastereoisomers was carried out by preparative thin layer chromatography (silica gel, 20% ether in hexanes) leading to pure 258 (270 mg, 64%).

Synthesis of tetra(Silylether) 259 as illustrated in Figure 38. Compound 258 (275 mg, 0.33 mmol) was dissolved in CH2Cl2 (5.0 mL), cooled to 0 °C and treated with 2,6-lutidine (76 mL, 0.66 mmol, 2.0 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (88 mL, 0.39 mmol, 1.2 equiv). After stirring for 2 h at 0 °C, the reaction mixture was quenched with aqueous HCl (5 mL, 1.0 N solution) and the aqueous phase was extracted with CH2Cl2 (3 x 5 mL). The combined organic solution was washed with brine (5 mL), dried (MgSO4) and concentrated under reduced pressure. Purification by flash column chromatography (silica gel, 3% ether in hexanes) provided tetra(silylether) 259 (300 mg, 96%) as a colorless oil.

Synthesis of Alcohol 260 as illustrated in Figure 38.
Alcohol 260 (200 mg, 85%) was obtained from compound 259 (264
mg, 0.28 mmol) according to the procedure described above for
223.

5

Synthesis of Aldehyde 261 as illustrated in Figure 38.
Oxidation of Alcohol 260. To a solution of oxalyl chloride
(54 mL, 0.61 mmol, 2.0 equiv) in CH2Cl2 (5.0 mL) was added
dropwise DMSO (86 mL, 1.21 mmol, 4.0 equiv) at -78 °C. After
10   stirring for 15 min at -78 °C, a solution of alcohol 260 (255
mg, 0.305 mmol, 1.0 equiv) in CH2Cl2 (2.0 mL) was added
dropwise at -78 °C over a period of 5 min. The solution was
stirred at -78 °C for 30 min, and then Et3N (250 mL, 1.82
mmol, 6.0 equiv) was added. The reaction mixture was allowed
15   to warm to 0 °C over a period of 30 min and then ether (20
mL) was added, followed by saturated aqueous NH4Cl solution
(10 mL). The organic phase was separated and the aqueous
phase was extracted with ether (2 x 10 mL). The combined
organic solution was dried (MgSO4), filtered and concentrated
20   under reduced pressure. Purification by flash column
chromatography (silica gel, 20% ether in hexanes) provided
aldehyde 261 (241 mg, 95%) as a colorless oil.

Synthesis of Carboxylic Acid 262 as illustrated in
25   Figure 38. Oxidation of Aldehyde 261. Aldehyde 261 (224
mg, 0.29 mmol), tBuOH (5.0 mL), isobutylene (5.0 mL, 2 M
solution in THF, 10.0 mmol), H2O (1.0 mL), NaClO2 (90 mg,
0.86 mmol, 3.0 equiv) and NaH2PO4 (60 mg, 0.43 mmol, 1.5
equiv) were combined and stirred at room temperature for 1 h.

The reaction mixture was concentrated under reduced pressure and the residue was subjected to flash column chromatography (silica gel, 6% MeOH in CH2Cl2) to afford carboxylic acid 262 (220 mg, 90%).

Synthesis of Hydroxy Acid 263 as illustrated in Figure 38. Selective Desilylation of 262. A solution of tris(silyl) ether 262 (300 mg, 0.36 mmol) in THF (7.0 mL) at 25 °C was treated with TBAF (2.2 mL, 1 M solution in THF, 2.2 mmol, 6.0 equiv). After stirring for 8 h, the reaction mixture was diluted with EtOAc (10 mL) and washed with aqueous HCl (10 mL, 1 N solution). The aqueous solution was extracted with EtOAc (4 x 10 mL) and the combined organic phase was washed with brine (10 mL), dried (MgSO4) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH2Cl2) to provide hydroxy acid 263 (203 mg, 78%) as a yellow oil.

Synthesis of Lactone 264 as illustrated in Figure 38. Macrolactonization of Hydroxy Acid 263. A solution of hydroxy acid 263 (1.0 eq) in THF (0.07 M) was treated at 0 °C with Et3N (2.2 equiv) and 2,4,6-trichlorobenzoyl chloride (1.3 equiv). The reaction mixture was stirred at 0 °C for 1 h, and then added to a solution of 4-DMAP (2.0 equiv) in toluene (0.002 M) at 25 °C and stirred at that temperature for 6 h. The solvents were removed in vacuo, and the crude product obtained was suspended in 40% ether in hexanes and filtered through silica gel. Concentration, followed by

preparative thin layer chromatography (silica gel, 5% MeOH in CH2C12), gave pure lactone 264 (77%).

Synthesis of Triol 265 as illustrated in Figure 39.
HF.pyr (0.25%) was carefully added to a solution of 264 (1.0 eq.) in THF (0.05 M) and the reaction mixture stirred for 24 hours at 25 °C. Aqueous saturated NaHCO3 solution was added followed by extraction with ethyl acetate. The organic phase was dried (MgSO4) and concentrated. The crude mixture was purified by flash column chromatography (silica gel, 5% MeOH in CH2C12) to provide triol 265 (78%).

Synthesis of Epoxyde 266 as illustrated in Figure 39.
The epoxidation of 265 according to the procedure described above for 232 led to epothilone 266.

What is claimed:

1.   A method for synthesizing an epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

which comprises the following steps:
    Step A: condensing a keto acid represented by the following structure:

with an aldehyde represented by the following structure:

-244-

wherein R$_5$ is selected from the group consisting of tert-
butyldimethylsilyl and trimethylsilyl, for producing a
carboxylic acid with a free hydroxyl moiety represented by
the following structure:

; then

Step B: derivatizing the free hydroxyl moiety of
said carboxylic acid of Step A with a derivatizing agent
represented by the formula R$_2$-X wherein R$_2$-X is selected
from the group consisting of tert-butyldimethylsilyl
chloride, tert-butyldimethylsilyl triflate, trimethylsilyl
chloride, trimethylsilyl triflate, methyl iodide, methyl
sulfate, acetic anhydride, acetic acid, acetyl chloride,
benzoic acid, benzoyl chloride, and 2-(tert-
butoxycarbonyloxyimino)-2-phenylacetonitrile for producing
a derivatized carboxylic acid represented by the following
structure:

; then

Step C: regioselectively deprotecting the R$_5$
protected hydroxyl moiety of the derivatized carboxylic
acid of said step B for producing a hydroxy acid with the
following structure:

; then

Step D: macrolactonizing the hydroxy acid of said Step C for producing a macrolide with the following structure:

; and then

Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

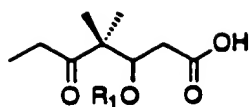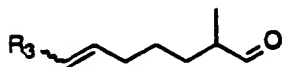2.   A method for synthesizing an epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:

-251-

which comprises:
        Step A: condensing a keto acid represented by the following structure:

with an aldehyde represented by the following structure:
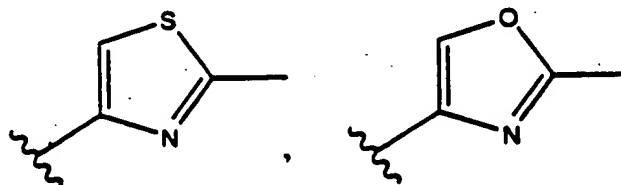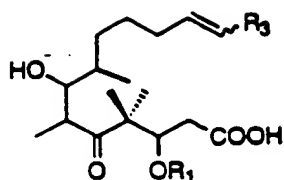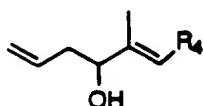

wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$-(solid phase support), for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:

; then

        Step B: esterifying the carboxylic acid of said Step A with a secondary alcohol represented by the following structure:
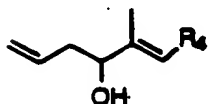
for producing an ester with a free hydroxyl moiety represented by the following structure:

; then

Step C: derivatizing the free hydroxyl moiety of said ester of Step B with a derivatizing agent represented by the formula R₂-X wherein R₂-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized ester represented by the following structure:

; then

Step D: metathesizing the derivatized ester of said Step C with an organo-metallic catalyst for producing a macrolide with the following structure:

; and then

Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

3. Th method as described in Claim 2 wherein the organo-metallic catalyst is selected from th group consisting of bis(tricyclohexylphosphine)benzylidine ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

4. The method as described in Claim 3 wherein the solid support is selected from the group consisting of Merrifield resin, PEG-polystyrene, hydroxymethyl polystyrene, formyl polystyrene, aminomethyl polystyrene and phenolic polystyrene.

5. A method for synthesizing an epothilone analog represented by the following structure:
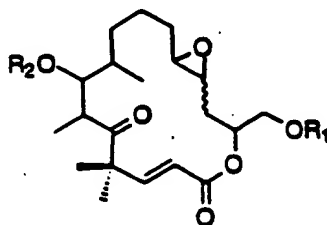
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:
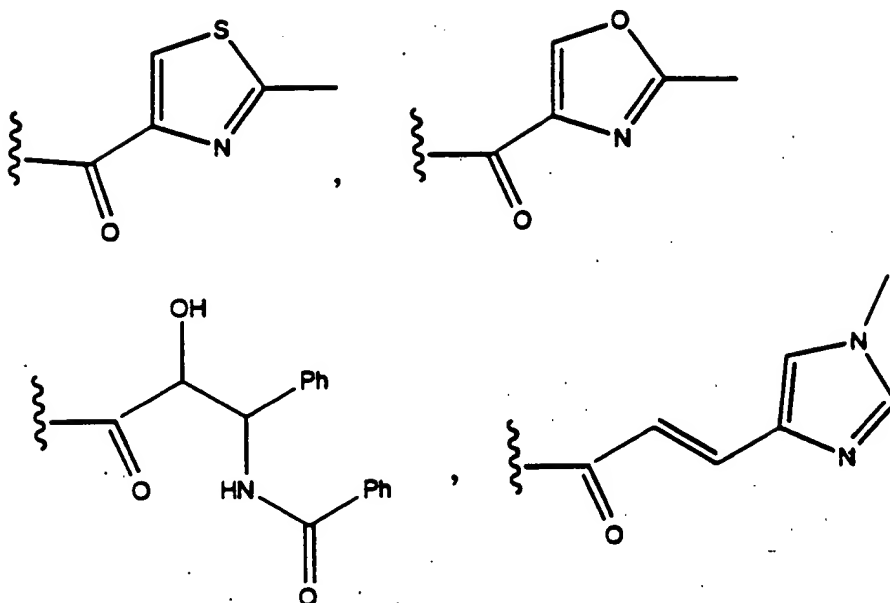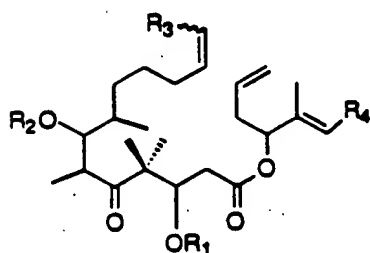
wherein R_2 is selected from the group consisting of, hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl;
which comprises the following steps:

Step A: esterifying a keto acid represented by the following structure:
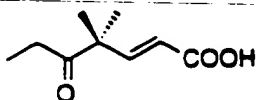
with an alcohol represented by the following structure:
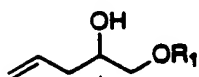
for producing an ester represented by the following structure:
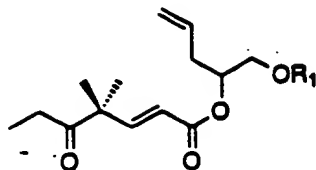
; then

Step B: condensing the ester of said Step A with an aldehyde represented by the following structure:
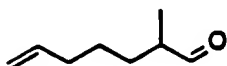
for producing a bis-terminal olefin with the following structure:
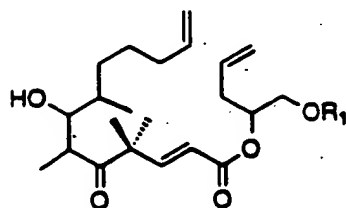
; then

Step C: metathesizing the bis-terminal olefin of said Step B with an organo-metallic catalyst for producing a macrocyclic lactone with a free hydroxyl moiety represented by the following structure:
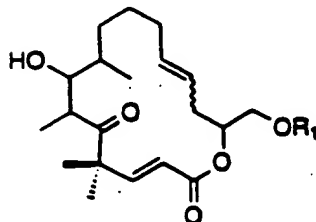
; then

Step D: derivatizing the free hydroxyl of the macrocyclic lactone of Step C with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of hydrogen, tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl

chl ride, and 2-(tert-butoxycarbonyloxyimino)-2-
phenylacet nitrile for producing a derivatized macrolide
with the following structure:
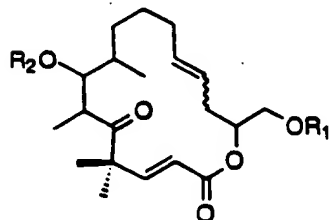
; and then

Step E: epoxidizing the derivatized macrolide of
said Step D for producing the epothilone analog.

6.   The method as described in Claim 5 wherein the
organo-metallic catalyst is selected from the group
consisting of bis(tricyclohexylphosphine)benzylidine
ruthenium dichloride, and 2,6-diisopropylphenylimido
neophylidenemolybdenum bis(hexafluoro-t-butoxide).

7.   A method for synthesizing an epothilone analog
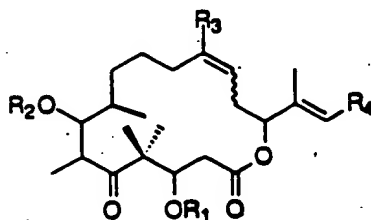represented by the following structure:

wherein R₁ is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
acetyl, benzoyl, and tert-butoxycarbonyl; wherein R₂ is
selected from the group represented by the following
strucutures:

which comprises the following steps:

Step A: condensing a keto acid represented by the following structure:

with an aldehyde represented by the following structure:

for producing a carboxylic acid with a free hydroxyl moiety represented by the following structure:

; then

Step B: derivatizing the free hydroxyl moiety of said carboxylic acid of Step A with a derivatizing agent represented by the formula R_1-X wherein R_1-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:

; then

Step C: esterifying the derivatized carboxylic acid of said Step B with an alcoh1 represented by the following structure:
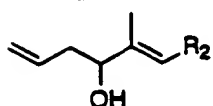
for producing a bis-terminal olefin with the following structure:
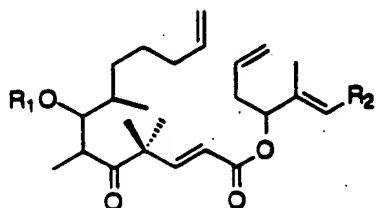
; and then

Step D: metathesizing the bis-terminal olefin of said Step C with an organo-metallic catalyst for producing a macrocyclic lactone with the following structure:
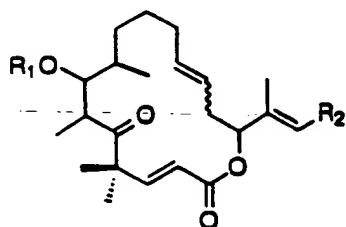
; then

Step E: epoxidizing the macrocyclic lactone of Step D producing the epothilone analog.

8. The method as described in Claim 7 wherein the organo-metallic catalyst is selected from the group consisting of bis(tricyclohexylphosphine)benzylidine ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

9. A method for synthesizing an epothilone analog represented by the following structure:
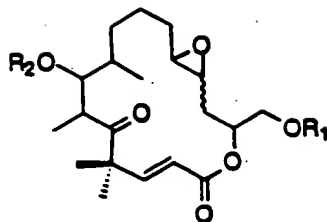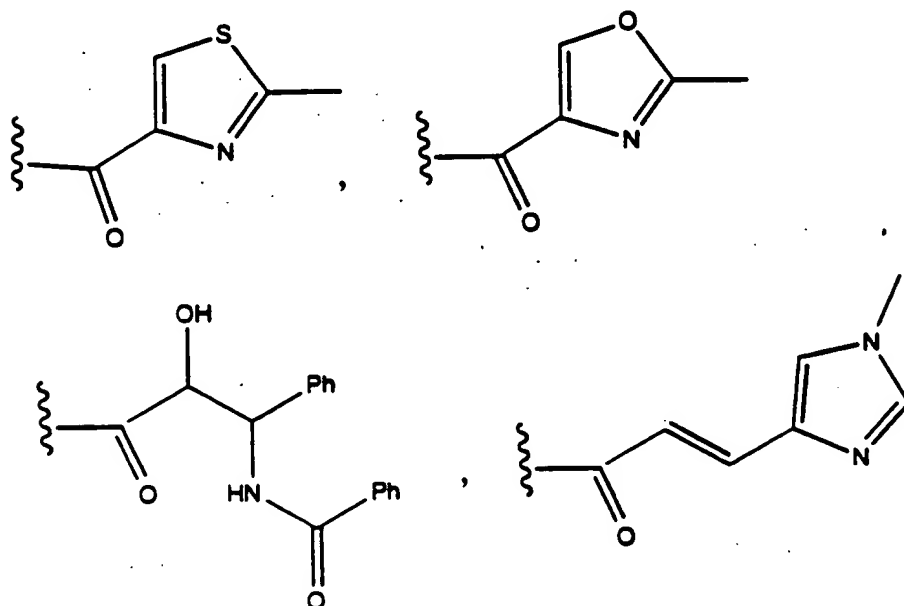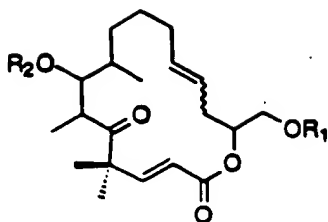
wherein R_1 is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
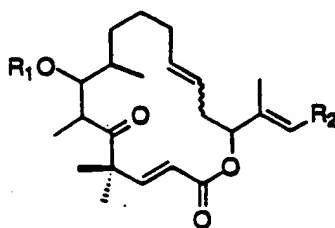acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is
selected from the group consisting of hydrogen, tert-
butyldimethylsilyl, trimethylsilyl, methyl, acetyl,
benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected
from the group consisting of hydrogen, methyl, -CH$_2$OH,
-CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R_4 is selected from the group
represented by the formulas:

which comprises the following steps:
    Step A: condensing a keto acid represented by the
following structure:

with an aldehyde represented by the following structure:

wherein R_5 is selected from the group consisting of tert-
butyldimethylsilyl and trimethylsilyl, for producing a

carboxylic acid with a free hydroxyl moiety represented by the f llowing structure:

; then

Step B: derivatizing the free hydroxyl moiety of said carboxylic acid of Step A with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized carboxylic acid represented by the following structure:

; then

Step C: regioselectively deprotecting the R_5 protected hydroxyl moiety of the derivatized carboxylic acid of said step B for producing a hydroxy acid with the following structure:

; then

Step D: macrolactonizing the hydroxy acid of said Step C for producing a macrolide having a Z-olefin with the following structure:
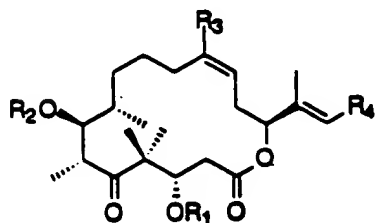
; and then

Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

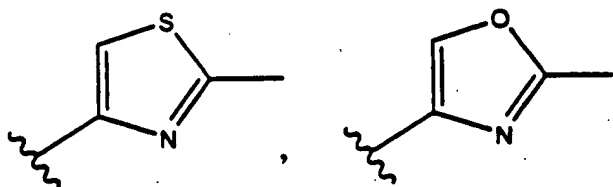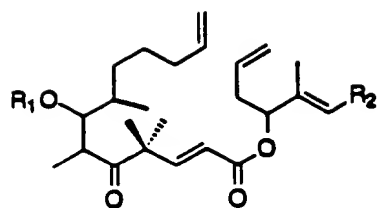10. A method for synthesizing an epothilone analog represented by the following structure:
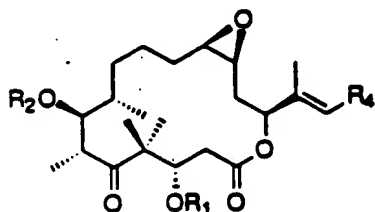
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:
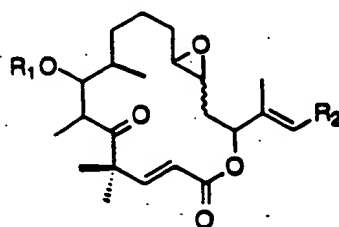

,

;
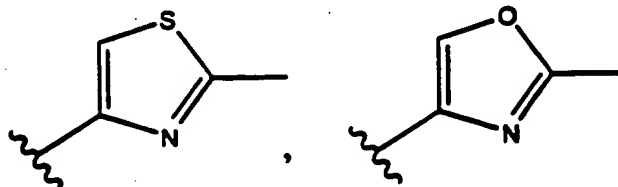
which comprises:

Step A: condensing a keto acid represented by the

following structure:
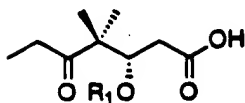
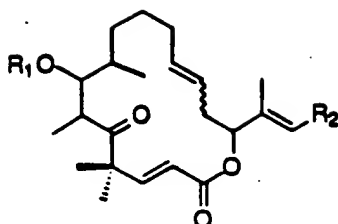5   with an aldehyde represented by the following structure:
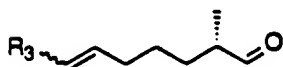
wherein R_3 is selected from the group consisting of H and
10         $(CH_2)_n$-(solid phase support) wherein $1 \leq n \leq 20$, for
producing a carboxylic acid with a free hydroxyl moiety
represented by the following structure:
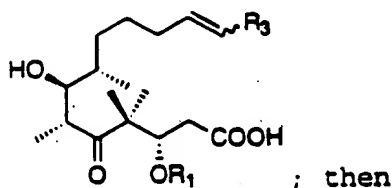
; then

15
          Step B: esterifying the carboxylic acid of said Step
A with a secondary alcohol represented by the following
structure:
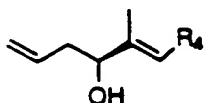
20

for producing an ester with a free hydroxyl moiety
represented by the following structure:

25   ; then

Step C: derivatizing the free hydroxyl moiety of said ester of Step B with a derivatizing agent represented by the formula R₂-X wherein R₂-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized ester represented by the following structure:

; then

Step D: Metathesizing the derivatized ester of said Step C with an organo-metallic catalyst for producing a macrolide with the following structure:

; and then

Step E: epoxidizing the macrolide of said Step D for producing the epothilone analog.

11. The method as described in Claim 10 wherein the organo-metallic catalyst is selected from the group consisting of bis(tricyclohexylphosphine)benzylidine ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide).

12. The method as described in Claim 10 wherein the solid support is selected from the group consisting of Merrifield resin, PEG-polystyrene, hydroxymethyl

polystyrene, formyl polystyrene, aminomethyl polystyrene and phenolic polystyrene.

13. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:
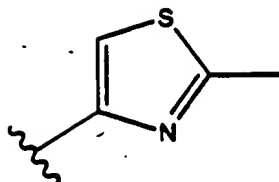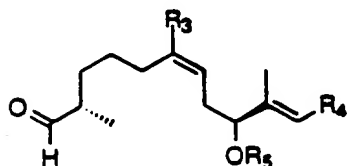

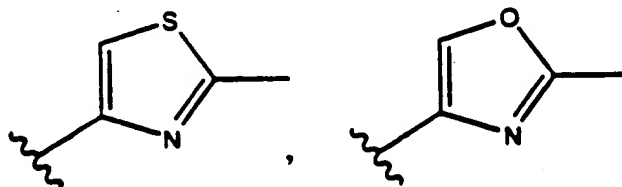wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, -CH$_2$OH, -CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R_4 is selected from the group represented by the formula:

wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl;

which comprises the step of condensing a keto acid represented by the following structure:

with an aldehyde represented by the following structure:

for producing the advanced intermediate.

14. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of. hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl; which comprises the step of derivatizing the free hydroxyl moiety of a carboxylic acid represented by the following structure:
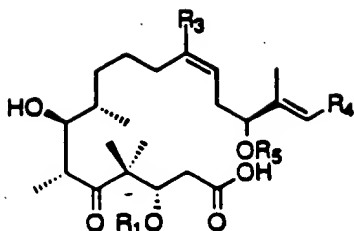
-24-

with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxy-carbonyl-oxyimino)-2-phenylacetonitrile for producing the advanced intermediate.

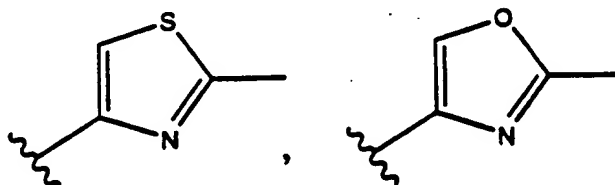15. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:
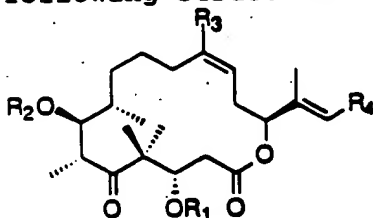

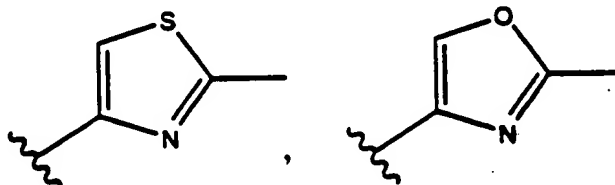wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:
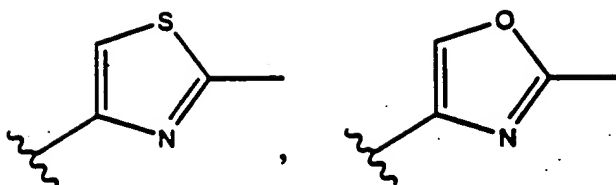
which comprises the step of regioselectively deprotecting a R_5 protected hydroxyl moiety of a derivatized carboxylic acid represented by the following structure:
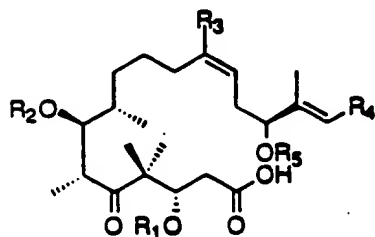
wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl, for producing the advanced intermediate.

16. A method for synthesizing an advanced intermediate for an epothilone analog represented by the following structure:
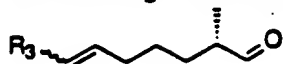

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, -CH$_2$OH, -CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R_4 is selected from the group represented by the formulas:
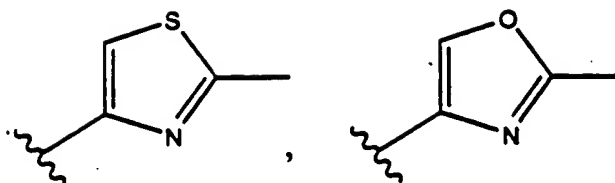
which comprises the step of macrolactonizing a hydroxy
acid represented by the following structure:
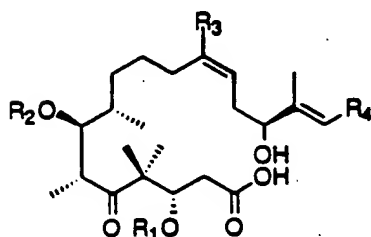
for producing the advanced intermediate.

17. A method for synthesizing an advanced
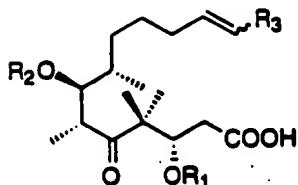intermediate for an epothilone analog represented by the
following structure:

wherein R_1 is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl; trimethylsilyl, methyl,
acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is
selected from the group consisting of hydrogen and $(CH_2)_n$-
(solid phase support);

which comprises:
    Step A: condensing a keto acid represented by the
following structure:

with an aldehyde represented by the following structure:

for producing the advanced intermediate.

18. A method for synthesizing an advanced intermediate of an epothilone analog represented by the following structure:
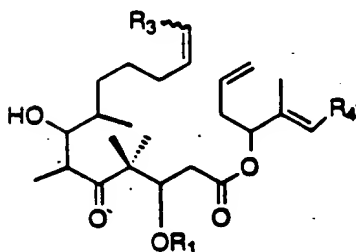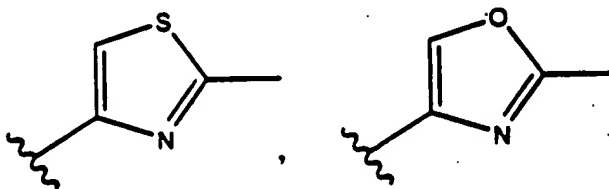

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$-(solid phase support); wherein R_4 is selected from the group represented by the formulas:

which comprises the step of esterifying a carboxylic acid with a free hydroxyl moiety represented by the following structure:

with a secondary alcohol represented by the following
structure:

for producing the advanced intermediate.

19. A method for synthesizing an advanced
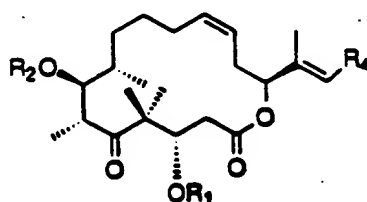intermediate for an epothilone analog represented by the
following structure:

wherein R_1 is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is
selected from the group consisting of hydrogen, tert-
butyldimethylsilyl, trimethylsilyl, methyl, acetyl,
benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected
from the group consisting of hydrogen and $(CH_2)_n$-(solid
phase support); wherein R_4 is selected from the group
represented by the formulas:
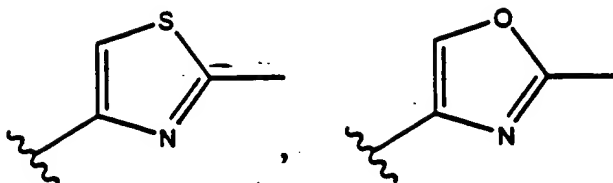
which comprises the step of derivatizing the free hydroxyl
moiety of an ester represented by the following structure:
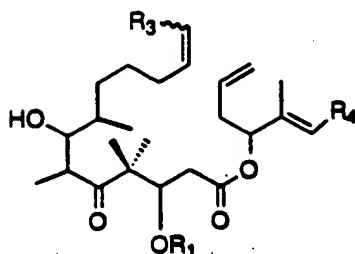
with a derivatizing agent represented by the formula R_2-X
wherein R_2-X is selected from the group consisting of
tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl
triflate, trimethylsilyl chloride, trimethylsilyl
triflate, methyl iodide, methyl sulfate, acetic anhydride,
acetic acid, acetyl chloride, benzoic acid, benzoyl
chloride, and 2-(tert-butoxycarbonyloxyimino)-2-
phenylacetonitrile for producing the advanced
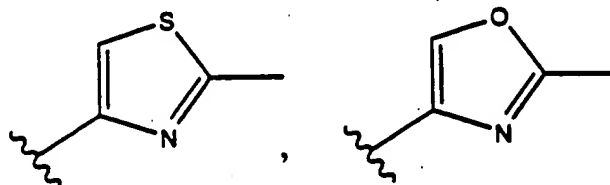intermediate.

20.   A method for synthesizing an advanced
intermediate of an epothilone analog represented by the
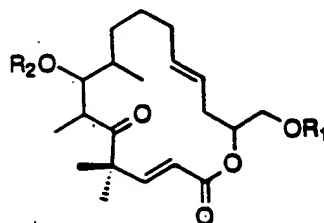following structure:

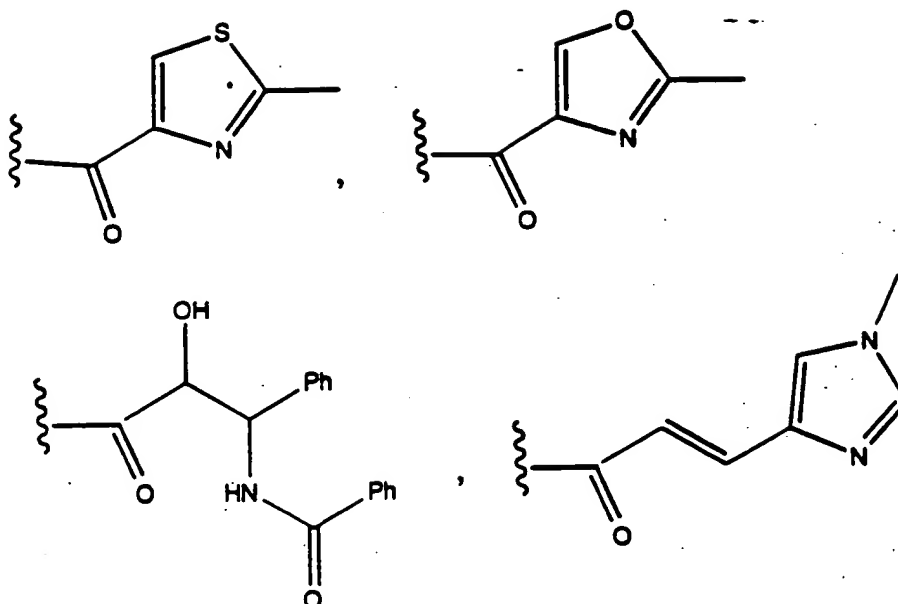wherein R_1 is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is
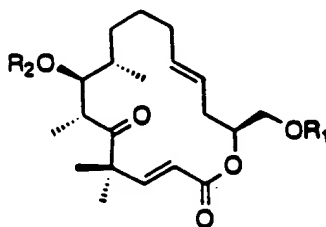selected from the group consisting of hydrogen, tert-

butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:

5
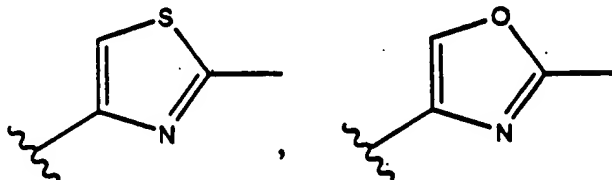
which comprises the step of metathesizing a derivatized ester represented by the following structure:

10

wherein R_3 is selected from the group consisting of $(CH_2)_n$-(solid phase support); with an organo-metallic catalyst selected from the group consisting of
15   bis(tricyclohexylphosphine)benzylidine ruthenium dichloride, and 2,6-diisopropylphenylimido neophylidenemolybdenum bis(hexafluoro-t-butoxide) for producing the advanced intermediate.

20   21.   A method for synthesizing an epothilone analog represented by the following structure:
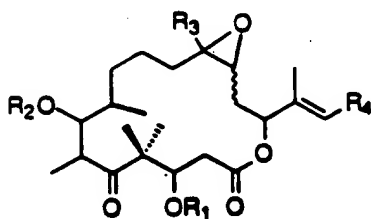
25   wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is
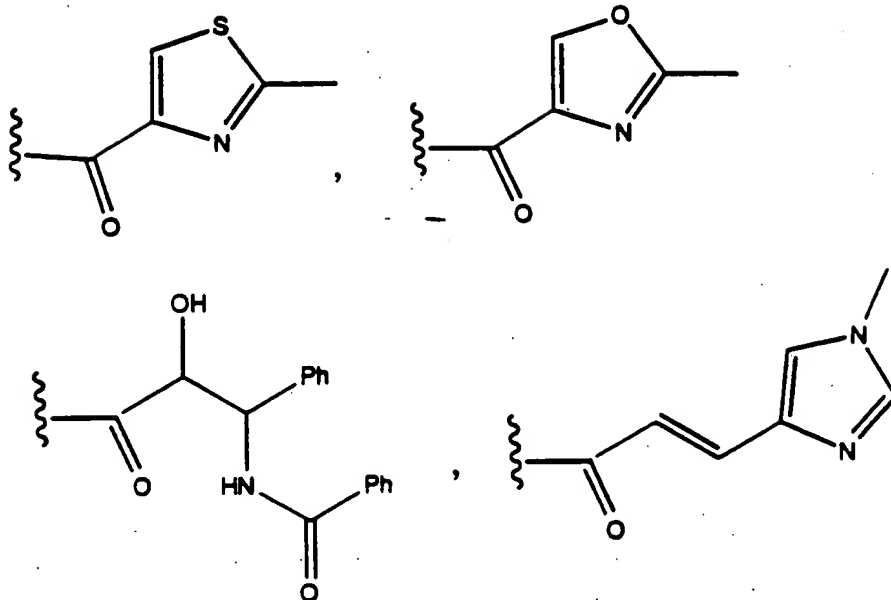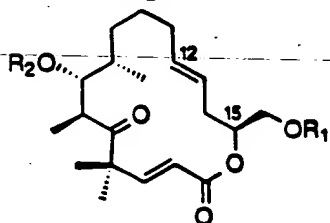
selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

which comprises the step of regioselectively epoxidizing a macrolide with the following structure:

for producing the epothilone analog.

22. A method for synthesizing an advanced intermediate of an epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formula:
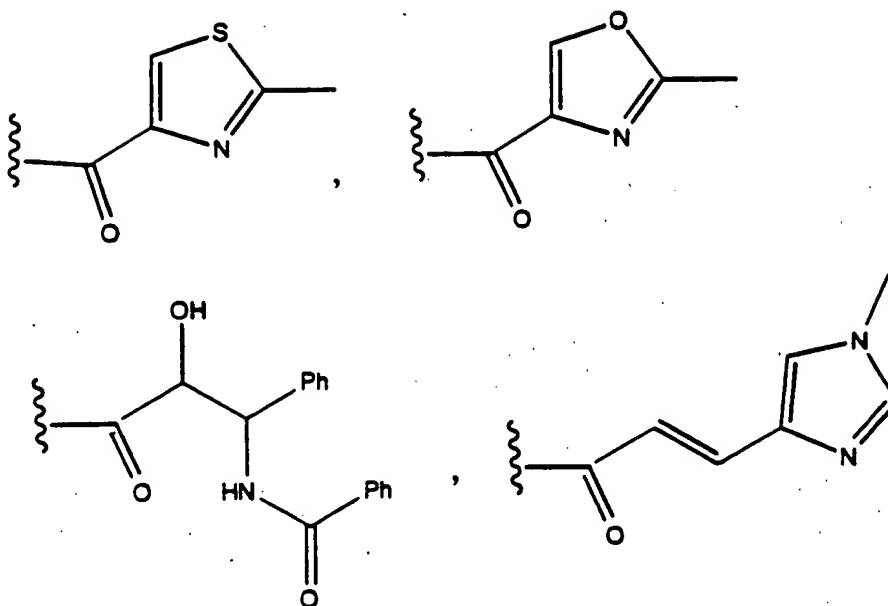
wherein R$_2$ is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
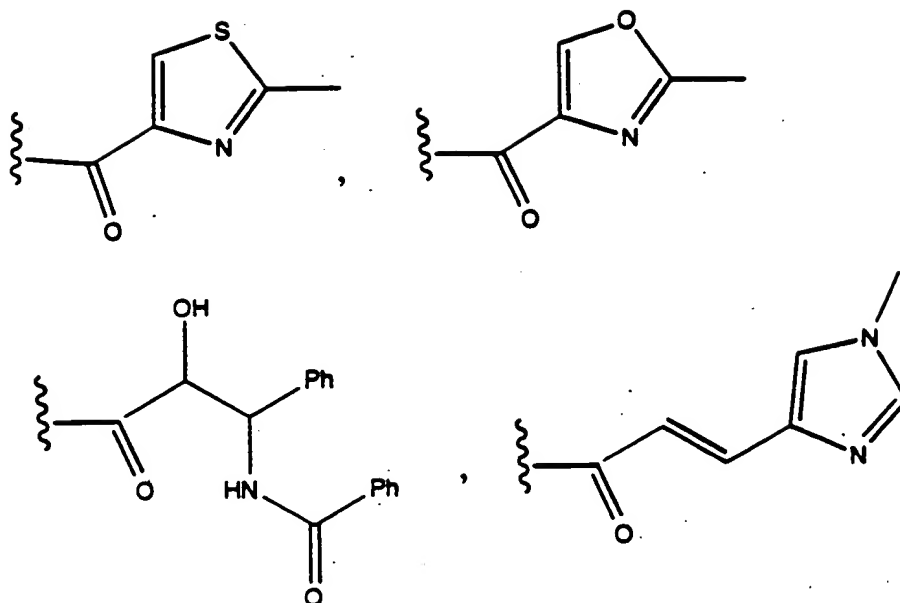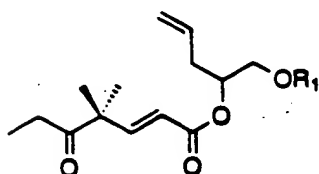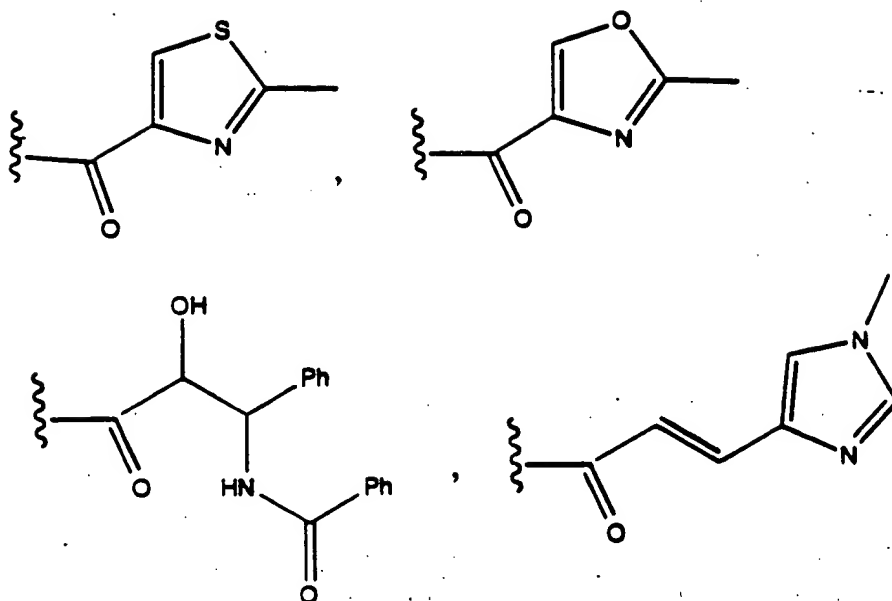acetyl, benzoyl, and tert-butoxycarbonyl;

which comprises the step of metathesizing a bis-terminal
olefin of represented by the following structure:
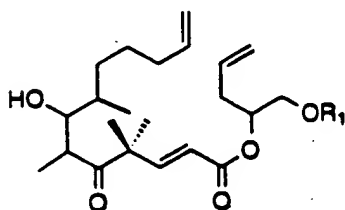
with an organo-metallic catalyst selected from the group
consisting of bis(tricyclohexylphosphine)benzylidine
ruthenium dichloride, and 2,6-diisopropylphenylimido
neophylidenemolybdenum bis(hexafluoro-t-butoxide) for
producing the advanced intermediate.

23. A method for synthesizing an epothilone analog
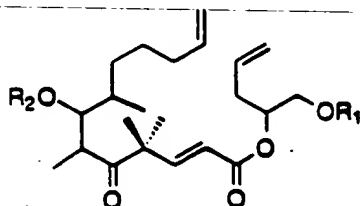represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, *tert*-butyldiphenylsilyl, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, *tert*-butoxycarbonyl and the group represented by the formula:

wherein R_2 is selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl;
which comprises the step of epoxidizing a derivatized macrolide represented by the following structure:

for producing the epothilone analog.

24. A method for synthesizing an advanced intermediate of an epothilone analog represented by the following structure:

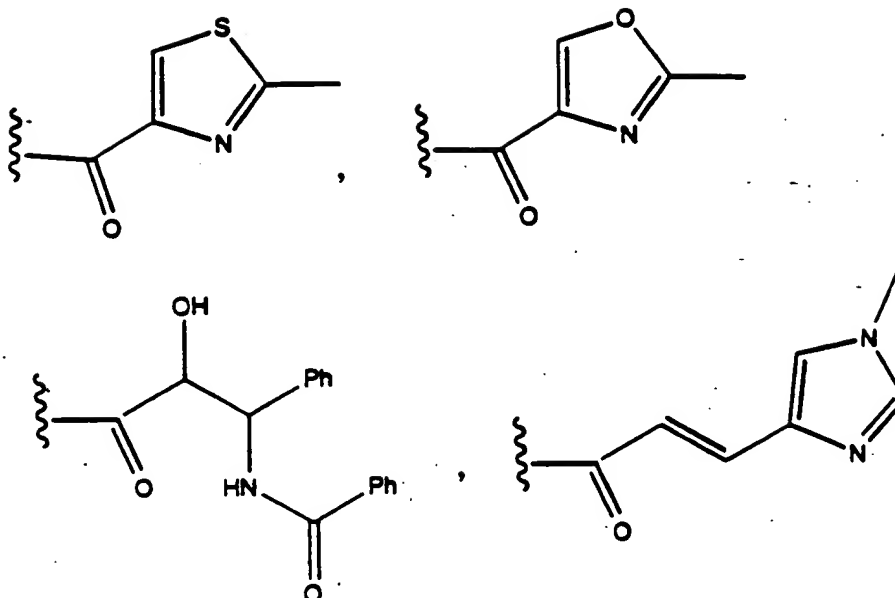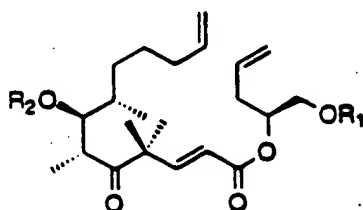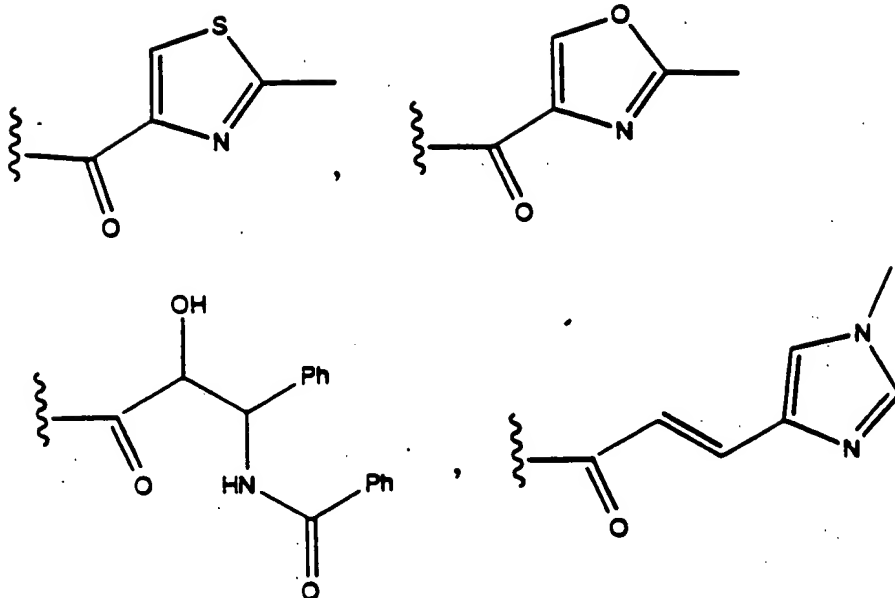wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein ; wherein R_2 is selected from the group represented by the following structures:

which comprises the step of metathesizing a bis-terminal olefin represented by the following structure:

with an organo-metallic catalyst selected from the group
consisting of bis(tricyclohexylphosphine)benzylidine
ruthenium dichloride, and 2,6-diisopropylphenylimido
neophylidenemolybdenum bis(hexafluoro-t-butoxide) for
producing the advanced intermediate.

25.   A method for synthesizing an epothilone analog
represented by the following structure:

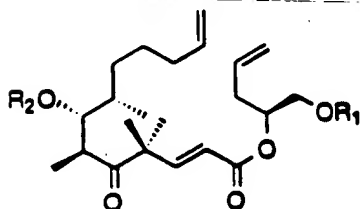
wherein R₁ is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
acetyl, benzoyl, and tert-butoxycarbonyl; wherein ;
wherein R₂ is selected from the group represented by the
following structures:
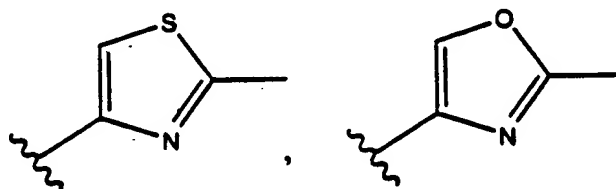
which comprises the step of epoxidizing a macrocyclic
lactone represented by the following structure:

for producing the epothilone analog.

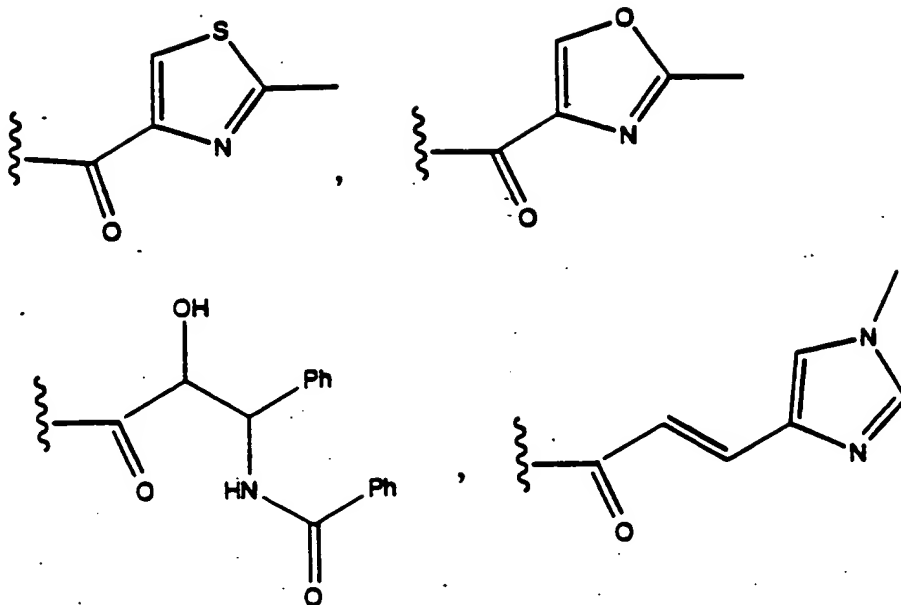5   26.   An epothilone analog represented by the following structure:
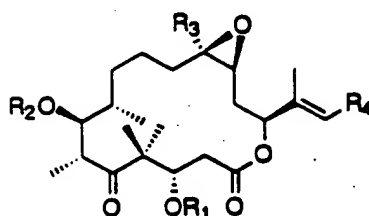
10   wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl,

15   benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

,
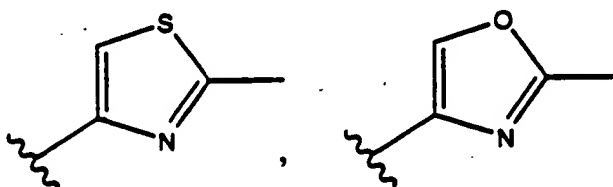
20

with the proviso that if R_3 is selected from the group consisting of methyl and hydrogen and R_4 is selected from the group represented by the formula:

25

than R_1 and R_2 cannot be simultaneously hydrogen.

27.   An epothilone analog intermediate represented by the following structure:
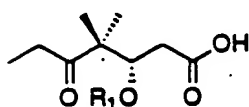
wherein R_1 is selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl.

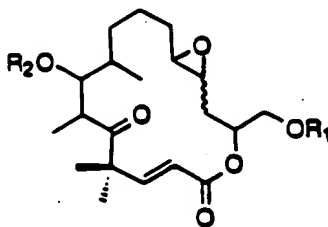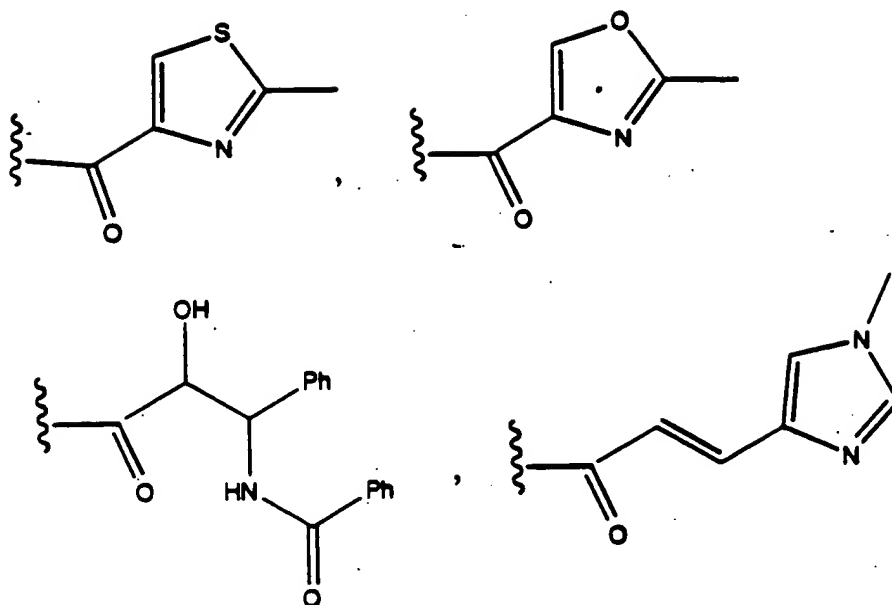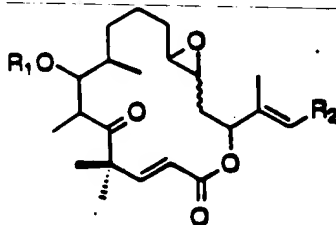28.   An epothilone analog intermediate represented by the following structure:

wherein R_3 is selected from the group consisting of hydrogen, methyl, -CH$_2$OH, -CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R_4 is selected from the group represented by the formula:

and wherein R_5 is selected from the group consisting of *tert*-butyldimethylsilyl and trimethylsilyl.

29. An epothilone analog intermediate represented by the
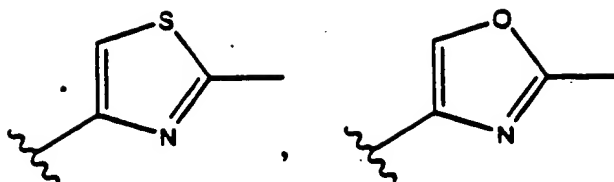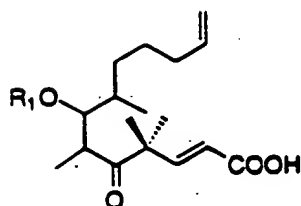following structure:

wherein R_1 is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is
selected from the group consisting of hydrogen, tert-
butyldimethylsilyl, trimethylsilyl, methyl, acetyl,
benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected
from the group consisting of hydrogen, methyl, -CH$_2$OH,
-CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R_4 is selected from the group
represented by the formula:

and wherein R_5 is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl and trimethylsilyl.

30. An epothilone analog intermediate represented by the
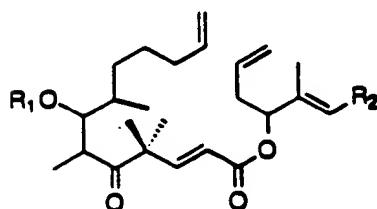following structure:

wherein R_1 is selected from the group consisting of
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,

acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoy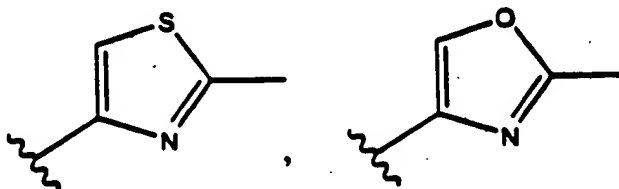l, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

,

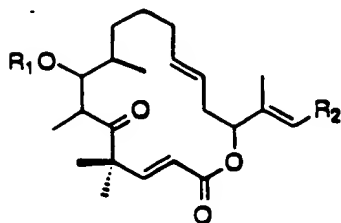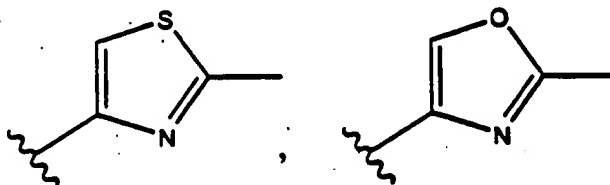31. An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

,

32. An epothilone analog intermediate represented by the

following structure:

wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$-(solid phase support).
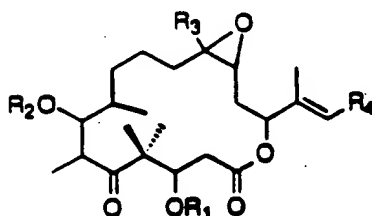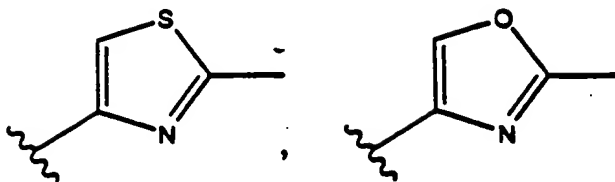
33.   An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert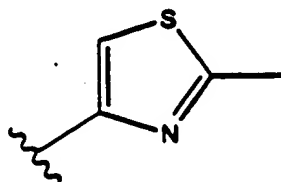-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl and wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$-(solid phase support).

34.   An epothilone analog intermediate represented by the following structure:
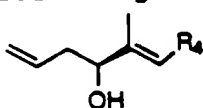
wherein R_4 is selected from the group represented by the formulas:

35. An epothilone analog intermediate represented by th following structure:
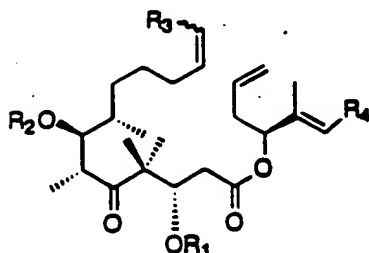
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

36. An epothilone analog intermediate represented by the following structure:
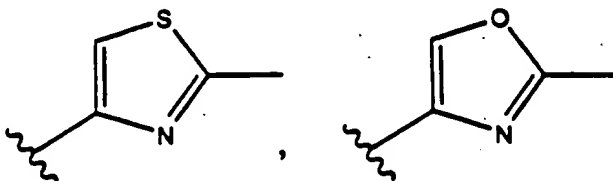

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is

-290-

selected from the group consisting of hydrogen, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and *tert*-butoxycarbonyl; wherein R_4 is selected from the group represented by the formulas:

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,

37. An epothilone analog represented by the following structure:

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wherein R_1 is selected from the group consisting of hydrogen, *tert*-butyldiphenylsilyl, *tert*-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, *tert*-butoxycarbonyl and the group represented by the formulas:

15

-27-

wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

38.   An epothilone analog represented by the following structure:

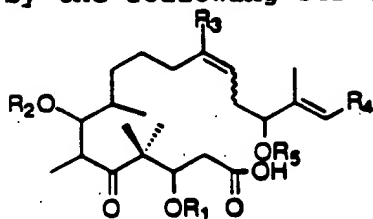wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:
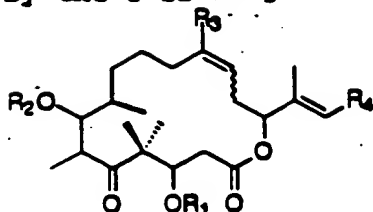
wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

39. An epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formula:

wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

40. An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:
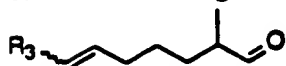
wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

41.   An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:

wherein R$_2$ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.
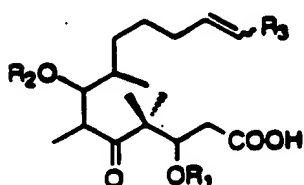
42. An epothilone analog intermediate represented by the following structure:

wherein R$_1$ is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formula:

wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

43. An epothilone analog intermediate represented by the following structure:

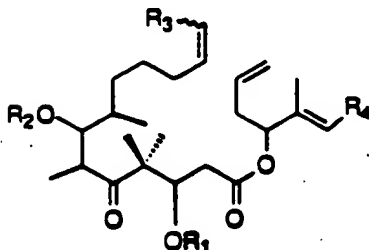wherein R_1 is selected from the group consisting of hydrogen, tert-butyldiphenylsilyl, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, tert-butoxycarbonyl and the group represented by the formulas:

wherein R_2 is selected from the group consisting of,
hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl,
acetyl, benzoyl, and tert-butoxycarbonyl.

44. An epothilone analog represented by the
following structure:

wherein R_1 is selected from the group consisting of
hydrogen, tert-butyldiphenylsilyl, tert-
butyldimethylsilyl, trimethylsilyl, methyl, acetyl,
benzoyl, tert-butoxycarbonyl and the group represented by
the formulas:

-42-

wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

45.   An epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following strucutures:
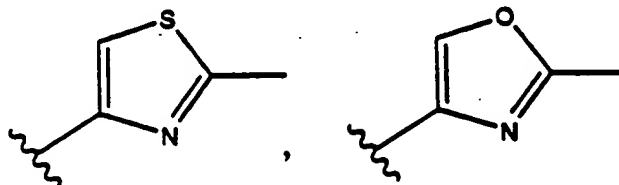
-3-

46. An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

47. An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group represented by the following strucutures:
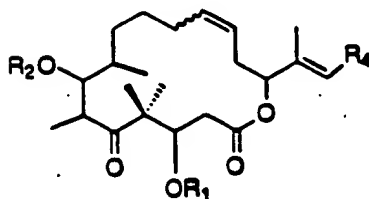
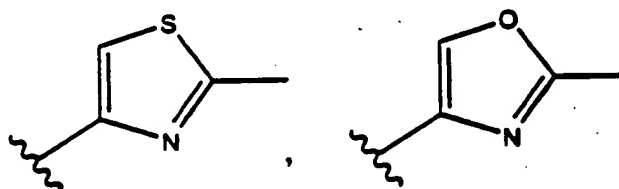48. An epothilone analog intermediate represented by the following structure:

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wherein R$_1$ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R$_2$ is
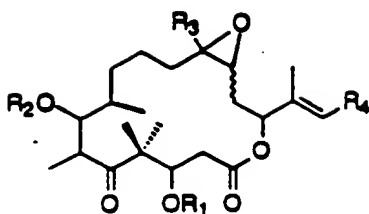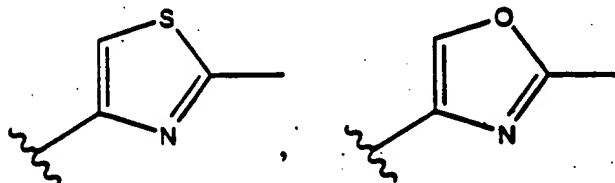
10 selected from the group represented by the following strucutures:

15 49. An epothilone analog represented by the following structure:

20 wherein R$_1$ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl;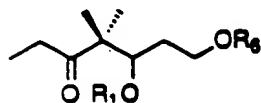 wherein R$_2$ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl,

25 benzoyl, and tert-butoxycarbonyl; wherein R$_3$ is selected from the group consisting of hydrogen, methyl, -CH$_2$OH, -CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R$_4$ is selected from the group

represented by the formulas:

,

with the proviso that if R_3 is selected from the group consisting of methyl and hydrogen and R_4 is represented by the formula:

then R_1 and R_2 cannot be simultaneously hydrogen.

50. An epothilone analog intermediate represented by the following structure:
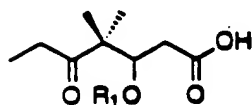
wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl.

51. An epothilone analog intermediate represented by the following structure:
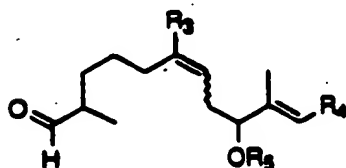
wherein R_3 is selected from the group consisting of

hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from th group represented by the formulas:
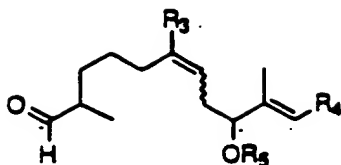

,

and wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl.

52. An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

,

and wherein R_5 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl and trimethylsilyl.

53. An epothilone analog intermediate represented

- 303 -

by the f 11 wing structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

54. An epothilone analog intermediate represented by the following structure:

wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$-(solid phase support).

55. An epothilone analog intermediate represented by the following structure:

-248-

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl and wherein R_3 is selected from the group consisting of hydrogen and $(CH_2)_n$-(solid phase support).

56. An epothilone analog intermediate represented by the following structure:
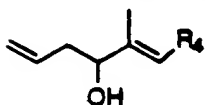
wherein R_4 is selected from the group represented by the formulas:

57. An epothilone analog intermediate represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected

-299-

from the group consisting of hydrogen, methyl, -CH$_2$OH, -CH$_2$Cl, and -CH$_2$CO$_2$H; wherein R$_4$ is selected from th group represented by the formulas:

,

58.   An epothilone analog intermediate represented by the following structure:

,

wherein R$_1$ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R$_2$ is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R$_4$ is selected from the group represented by the formulas:
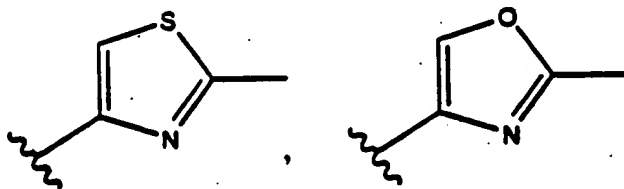

,

59.   A method for synthesizing an epothilone analog represented by the following structure:

-306-

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:
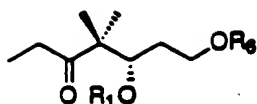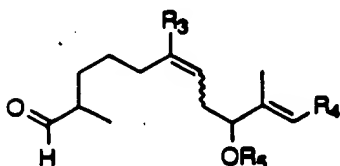

which comprises the following steps:

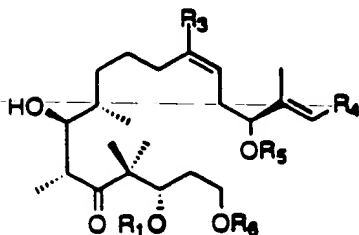Step A: condensing a keto acid represented by the following structure:

wherein R_6 is selected from the group consisting of tert-butyldimethylsilyl, trimethylsilyl, tert-butyldiphenylsilyl, methyl, hydrogen, triethylsilyl, and benzyl;
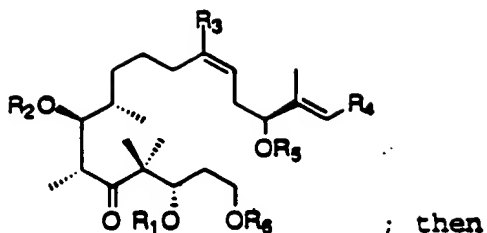
with an aldehyde represented by the following structure:

-301-

wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl, for producing a β-hydroxy ketone with a free hydroxyl moiety and a R_6 protected hydroxyl moiety represented by the following structure:
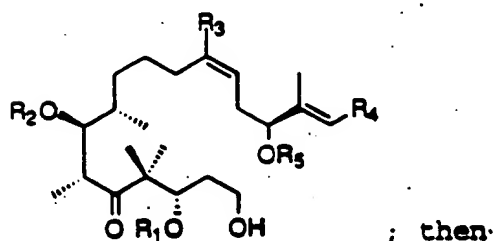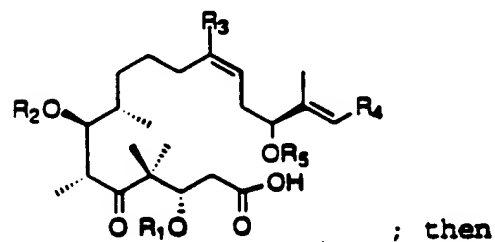

; then

Step B: derivatizing the free hydroxyl moiety of said β-hydroxy ketone of Step A with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized β-hydroxy ketone represented by the following structure:
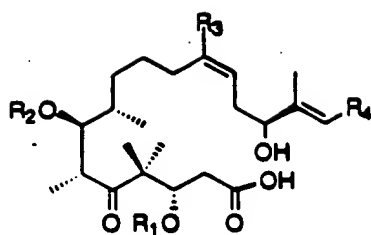

; then

Step C: regioselectively deprotecting the R_6 protected hydroxyl moiety of the derivatized β-hydroxy ketone of said step B for producing a terminal alcohol

-3-

with the following structure:

; then

Step D: oxidizing the terminal alcohol of said Step C for producing a derivatized carboxylic acid with a R_5 protected hydroxyl moiety with the following structure:
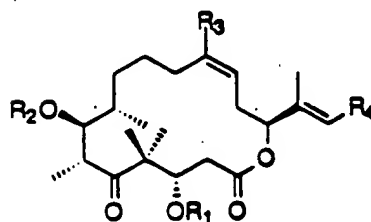

; then

Step E: regioselectively deprotecting the R_5 protected hydroxyl moiety of the derivatized carboxylic acid of said step D for producing a hydroxy acid with the following structure:

; then

Step F: macrolactonizing the hydroxy acid of said Step E for producing a macrolide with the following structure:

; and then

Step G: epoxidizing the macrolide of said Step F for producing the epothilone analog.

60. A method for synthesizing an epothilone analog represented by the following structure:

wherein R_1 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_2 is selected from the group consisting of hydrogen, tert-butyldimethylsilyl, trimethylsilyl, methyl, acetyl, benzoyl, and tert-butoxycarbonyl; wherein R_3 is selected from the group consisting of hydrogen, methyl, $-CH_2OH$, $-CH_2Cl$, and $-CH_2CO_2H$; wherein R_4 is selected from the group represented by the formulas:

,

which comprises the following steps:
Step A: condensing a keto acid represented by the following structure:

wherein R_6 is selected from the group consisting of tert-butyldimethylsilyl, trimethylsilyl, tert-butyldiphenylsilyl, methyl, hydrogen, triethylsilyl, and benzyl;

with an aldehyde represented by the following structure:

wherein R_5 is selected from the group consisting of tert-butyldimethylsilyl and trimethylsilyl, for producing a β-hydroxy ketone with a free hydroxyl moiety and a R_6 protected hydroxyl moiety represented by the following structure:

; then

Step B: derivatizing the free hydroxyl moiety of said β-hydroxy ketone of Step A with a derivatizing agent represented by the formula R_2-X wherein R_2-X is selected from the group consisting of tert-butyldimethylsilyl chloride, tert-butyldimethylsilyl triflate, trimethylsilyl chloride, trimethylsilyl triflate, methyl iodide, methyl sulfate, acetic anhydride, acetic acid, acetyl chloride, benzoic acid, benzoyl chloride, and 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile for producing a derivatized β-hydroxy ketone represented by the following structure:

_3o5_

; then

Step C: regioselectively deprotecting the R$_6$
protected hydroxyl moiety of the derivatized β-hydroxy
ketone of said step B for producing a terminal alcohol
with the following structure:

; then·

Step D: oxidizing the terminal alcohol of said Step
C for producing a derivatized carboxylic acid with a R$_5$
protected hydroxyl moiety with the following structure:

; then

Step E: regioselectively deprotecting the R$_5$
protected hydroxyl moiety of the derivatized carboxylic
acid of said step D for producing a hydroxy acid with the
following structure:

; then

Step F: macrolactonizing the hydroxy acid of said
Step E for producing a macrolide with the following
structure:

; and then

Step G: epoxidizing the macrolide of said Step F for
producing the epothilone analog.

Abstract of the Disclosure

Epothilone A, epothilone B, analogs of epothilone and libraries of epothilone analogs are synthesized. Epothilone A and B are known anticancer agents that derive their anticancer activity by the prevention of mitosis through the induction and stabilization of microtubulin assembly. The analogs of epothilone are novel. Several of the anlogs are demonstrated to have a superior cytotoxic activities as compared to epothilone A or epothilone B as demonstrated by their enhanced ability to induce the polymerization and stabilization of microtubules.

<u>PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY</u>

:REBY DECLARE THAT:

:esidence, post office address, and citizenship are as stated next to my name in
: A of page 2 here f.

:lieve I am the original, first, and s le inventor (if only one name is listed) or
original, first, and joint inventor (if plural names are listed) of the subject
:er which is claimed and for which a patent is sought on the invention entitled
:D AND SOLUTION PHASE SYNTHESIS OF EPOTHILONES A AND B AND LIBRARIES OF EPOTHILONE
:OGS___ the specification of which:
__ is attached hereto
_X_ was filed on _May 14, 1997_ as Application Serial No. _____
    and was amended on _____ (if applicable).

:reby state that I have reviewed and understand the contents of the above-identified
:ification, including the claims, as amended by any amendment referred to above.

:knowledge the duty to disclose information which is material to the examination of
: application in accordance with Title 37, Code of Federal Regulations, Sec.
:(a).

:reby claim foreign priority benefits under Title 35, United States Code, Sec. 119
any foreign application(s) for patent or inventor's certificate listed in PART B on
: 2 hereof and have also identified in PART B on page 2 hereof any foreign
lication for patent or inventor's certificate having a filing date before that of
application on which priority is claimed.

:reby claim the benefit under Title 35, United States Code, Sec. 120 of any United
:es application(s) listed in PART C on page 2 hereof and, insofar as the subject
:er of each of the claims of this application is not disclosed in the prior United
:es application in the manner provided by the first paragraph of Title 35, United
:es Code, Sec. 112, I acknowledge the duty to disclose material information as
ined in Title 37, Code of Federal Regulations, Sec. 1.56(a) which occurred between
filing date of the prior application and the national or PCT international filing
: of this application.

:reby declare that all statements made herein of my knowledge are true and that all
:ements made on information and belief are believed to be true; and further that
se statements were made with the knowledge that willful false statements and th
e so made are punishable by fine or imprisonment, or both, under Section 1001 of
le 18 of the United States Code and that such willful false statements may
pardize the validity of the application or any patent issued thereon.

lereby appoint the following as my attorneys or agents with full power of
stitution to prosecute this application and transact all business in the United
tes Patent and Trademark Office connected therewith:

glas A. Bingham   Reg. No. 32,457   Donald G. Le 'is   Reg. No. 28,636
mas Fitting   Reg. No. 34,163   Emily Holmes   Reg. No. P-40,652

se mailing address for this application i
                    THE SCRIPPS RESEARCH INSTITUTE
                    10550 North Torrey Pines Road
                    Mail Drop TPC 8
                    La Jolla, California 92037
    Pages 2 and 3 attached, signed, and made a part here f.

PATENT APPLICATION DECLARATION AND POWER OF ATTORNEY

A: Invent r Inf rmation And Signature

name of SOLE or FIRST invent r _____ Kyriacos Nicolaou _____

zenship _____ Post Office Address _____

dence (if different) _____

ntor's Signature:_____ Date:_____

name of SECOND joint inventor, if any_____ Yun He _____

zenship _____ Post Office Address _____

dence (if different) _____

nd Inventor's Signature:_____ Date:_____

name of THIRD joint inventor, if any_____ Sacha Ninkovic _____

zenship _____ Post Office Address _____

dence (if different) _____

d Inventor's Signature:_____ Date:_____

name of FOURTH joint inventor, if any_____ Joaquin Pastor _____

zenship _____ Post Office Address _____

dence (if different) _____

th Inventor's Signature:_____ Date:_____

name of FIFTH joint inventor, if any_____ Frank Roschangar _____

zenship _____ Post Office Address _____

dence (if different) _____

h Inventor's Signature:_____ Date:_____

name of SIXTH joint inventor, if any_____ Francisco Sarabia _____

zenship _____ Post Office Address _____

dence (if different) _____

h Inventor's Signature:_____ Date:_____

Page 1 ro hi h this is attached and from which this Page 2 continues.

name of SEVENTH joint inventor, if any___ Hans Vallberg _____

zenship _____ P st Office Address _____
_____

dence (if different) _____

nth Invent r's Signature:_____ Date:_____

name of EIGHTH joint inventor, if any___ Dionisios Vourloumis _____

zenship _____ Post Office Address _____
_____

dence (if different) _____

ith Inventor's Signature:_____ Date:_____

name of NINTH joint inventor, if any___ Nicolas Winssinger _____

zenship _____ Post Office Address _____
_____

dence (if different) _____

h Inventor's Signature:_____ Date:_____

l name of TENTH joint inventor, if any___ Zhen Yang _____

izenship _____ Post Office Address _____
_____

idence (if different) _____

h Inventor's Signature:_____ Date:_____

B: Prior Foreign Application(s)

ial No.   Country   Day/Month/Year Filed   Priority Claimed
                                                    ___ Yes ___ N

C: Claim For Benefit of Filing Date of Earlier U.S. Application(s)

ial No.   Filing Date   Status:
032,864   12/13/96   ___ Patented   _X_ Pending   ___ Abandoned

Pages 1 and 2 to which this is attached and from which this Page 3 continues.

\WP\FORMS\NOV0033P.PGA
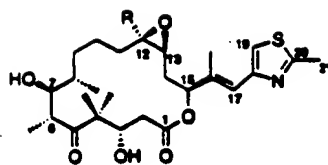
1: R = H, epothilone A
2: R = Me, epothilone B
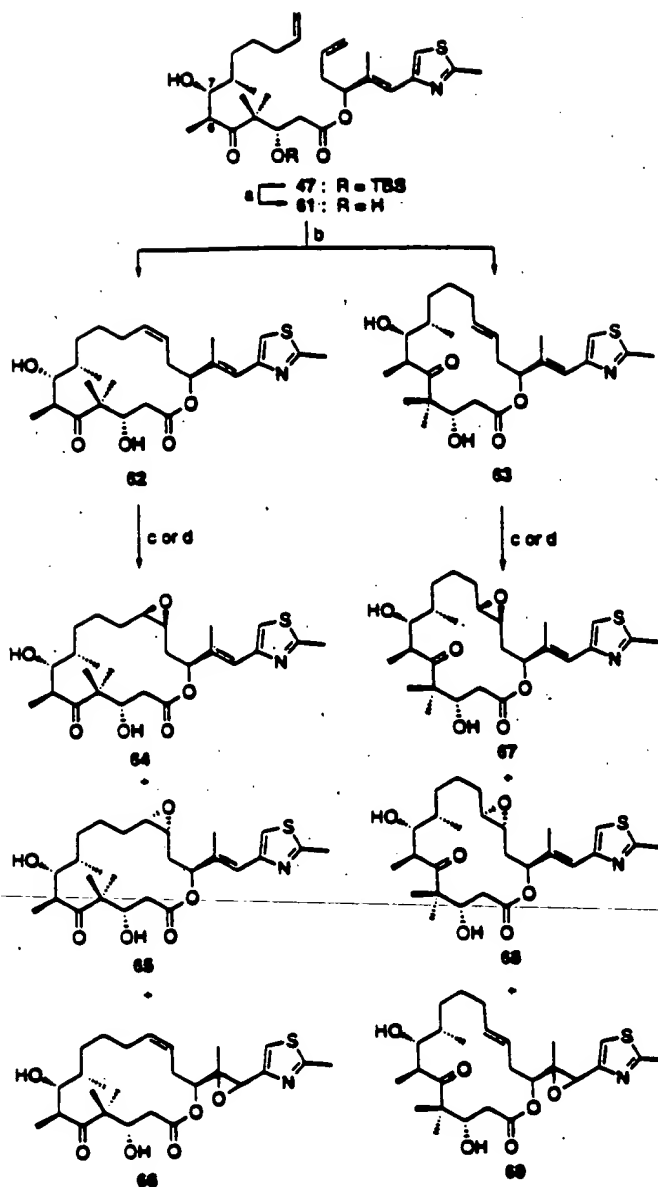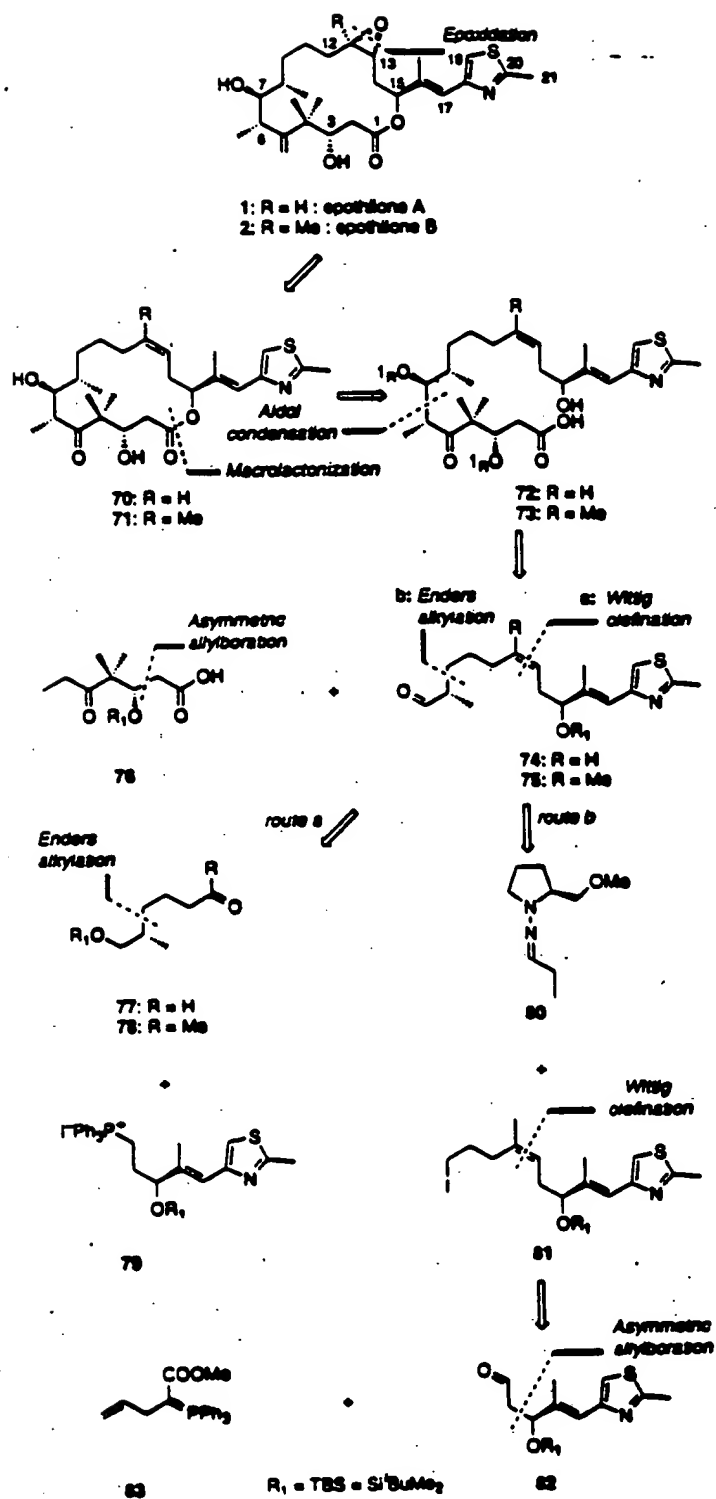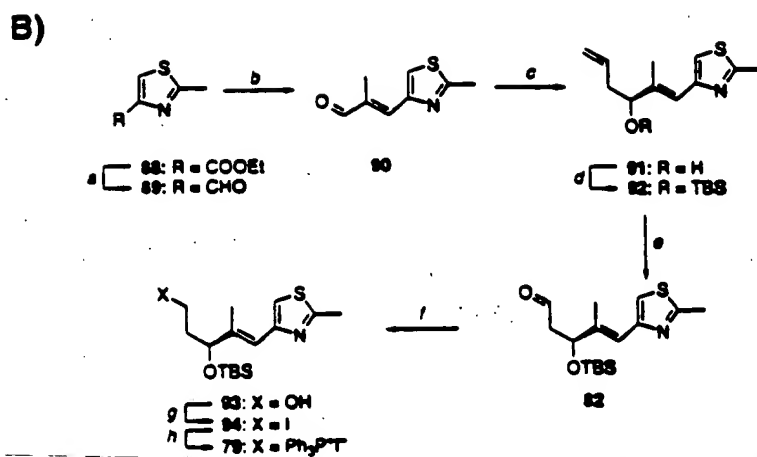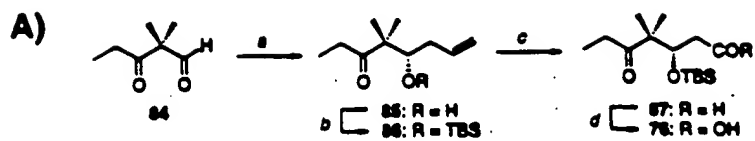
FIGURE 1
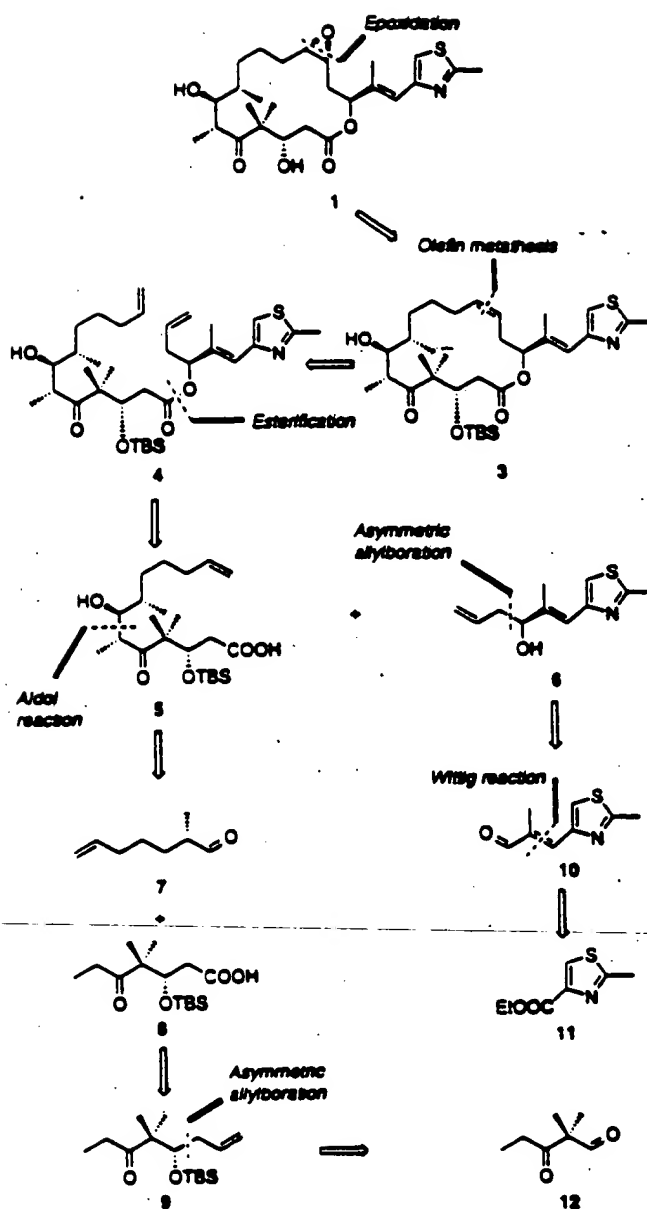
FIGURE 2
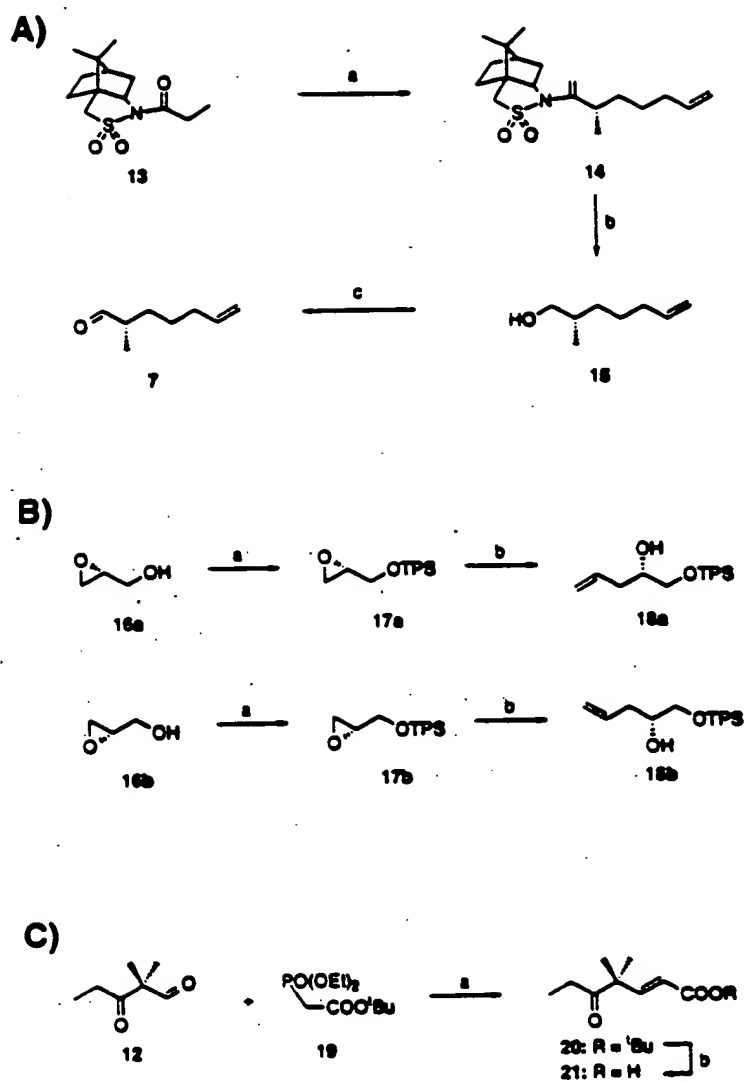
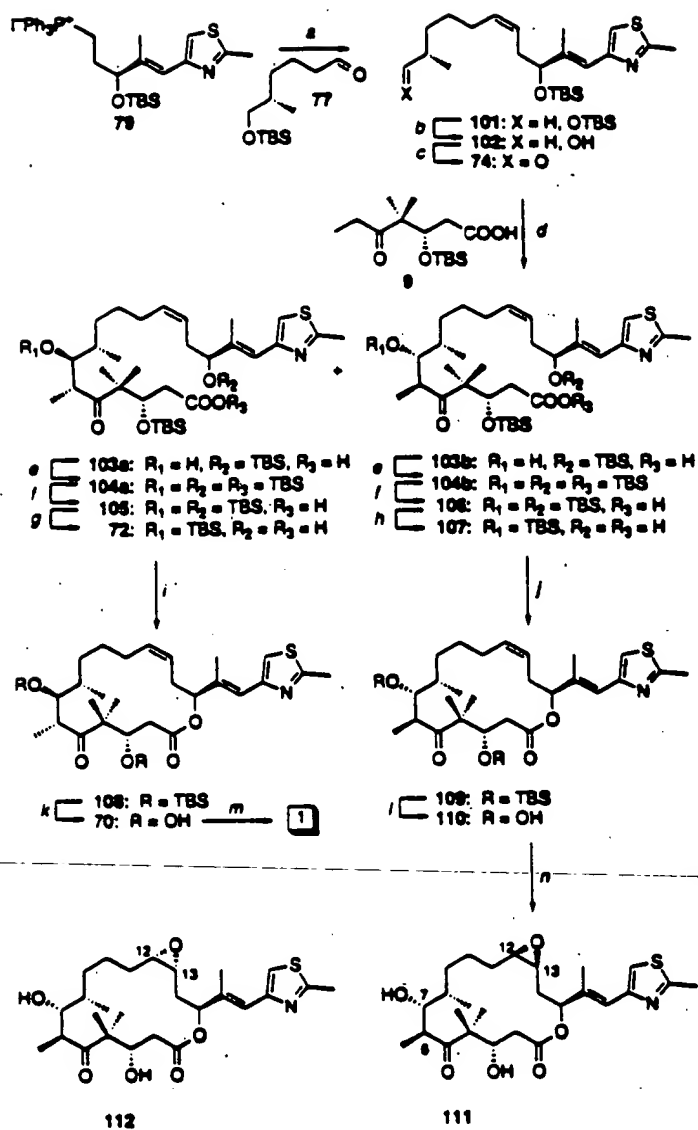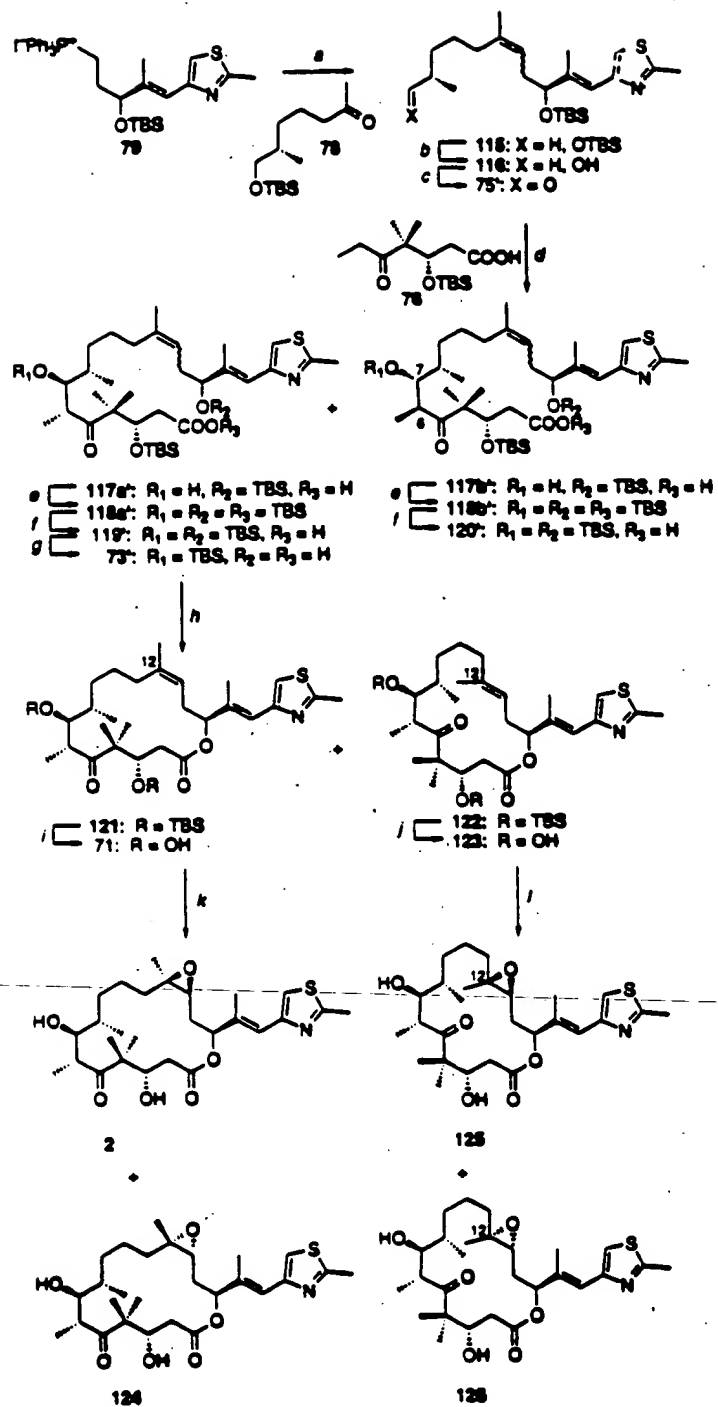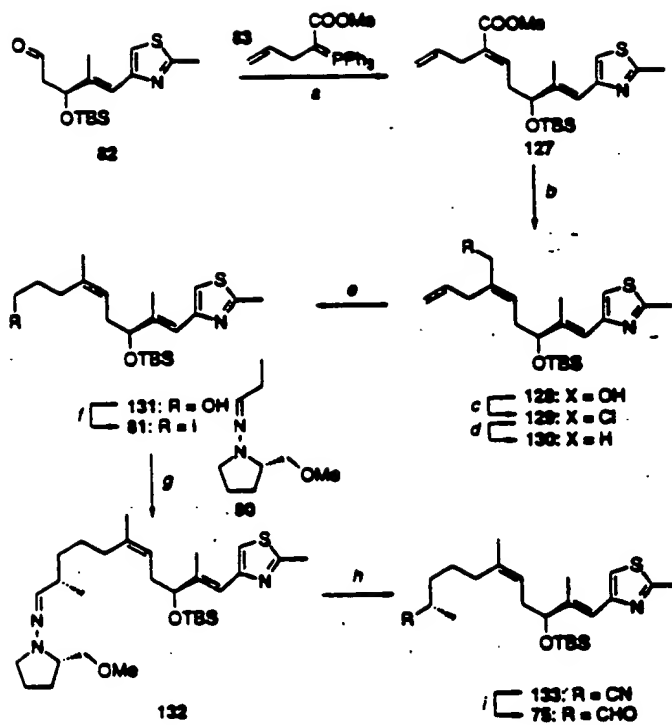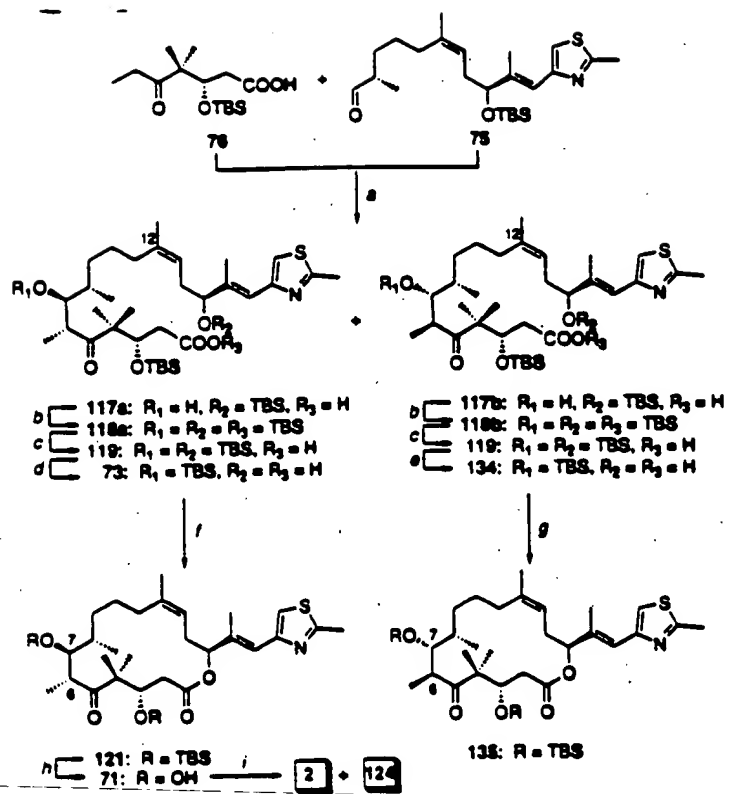FIGURE 3
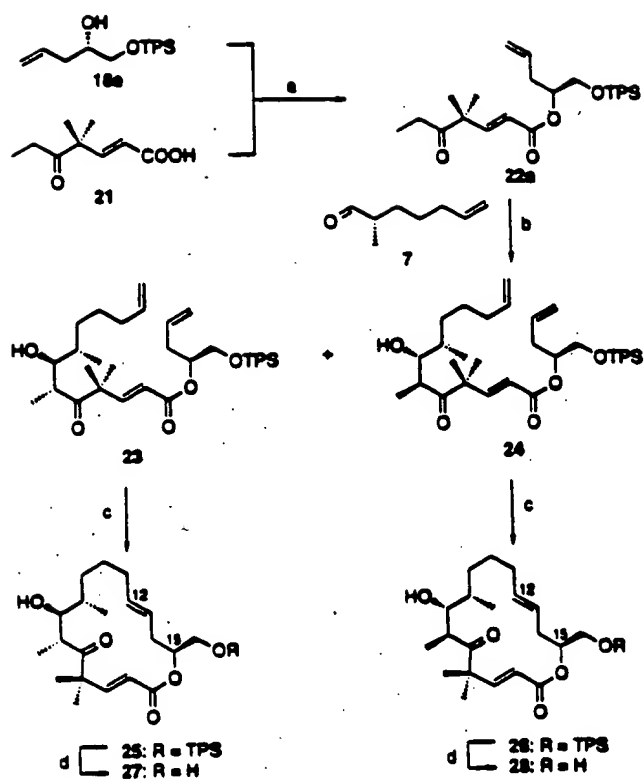
FIGURE 4
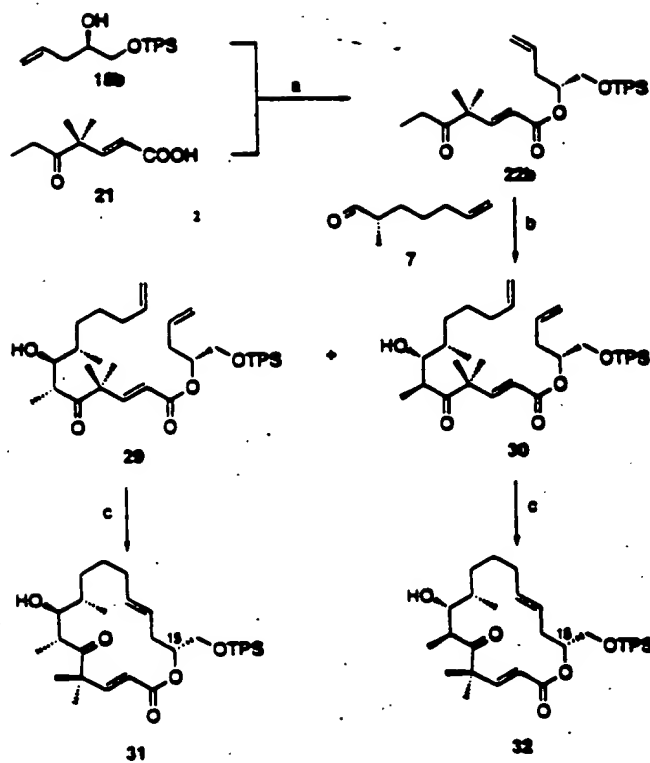
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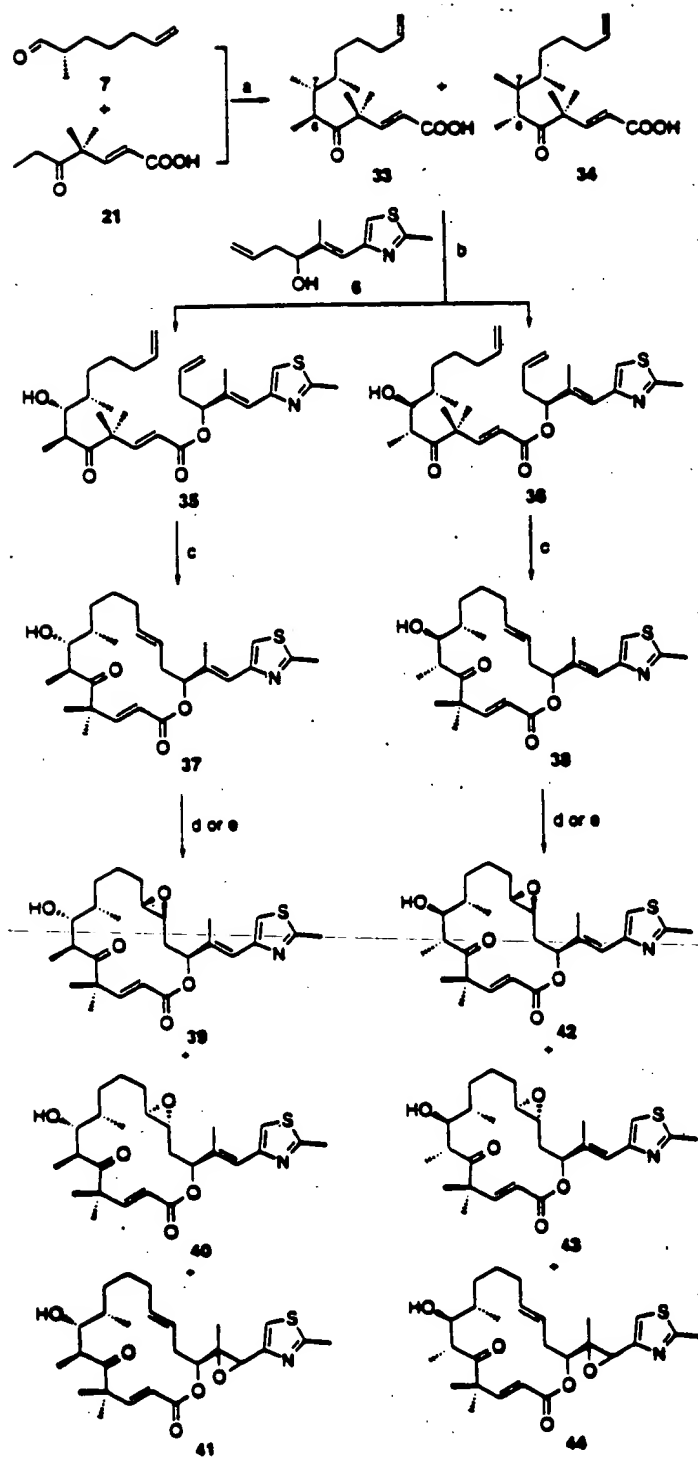
FIGURE 6

FIGURE 7

FIGURE 8

a, or b, or c

50

58

59

60

FIGURE 9

FIGURE 10

1: R = H : epothilone A
2: R = Me : epothilone B

70: R = H
71: R = Me

72: R = H
73: R = Me

76

74: R = H
75: R = Me

77: R = H
78: R = Me

80

79

81

83

R₁ = TBS = Si^tBuMe₂

82

FIGURE 11

A)

a: 85: R = H
b: 86: R = TBS

d: 87: R = H
78: R = OH

B)

a: 88: R = COOEt
89: R = CHO

90

d: 91: R = H
92: R = TBS

g: 93: X = OH
h: 94: X = I
75: X = Ph₃PT

82
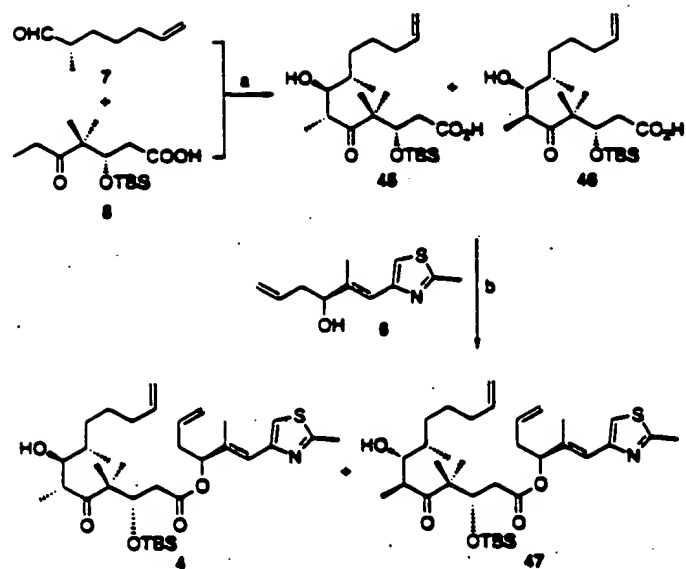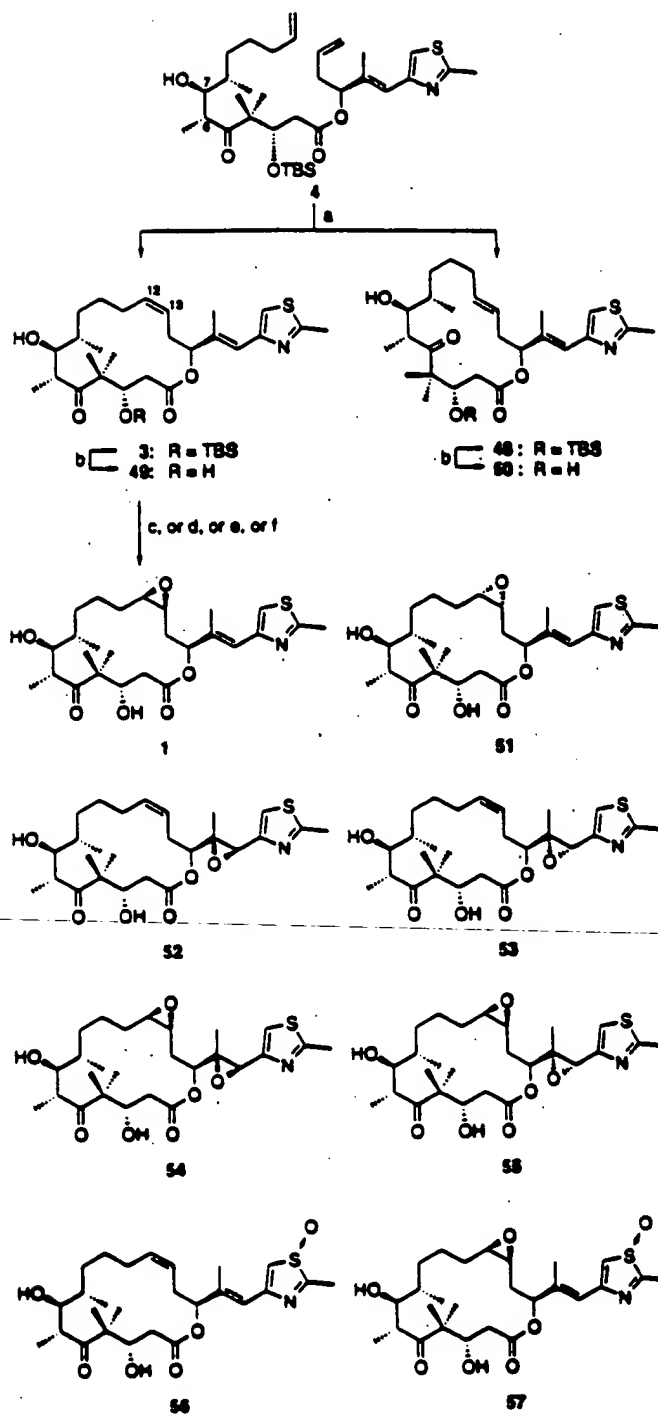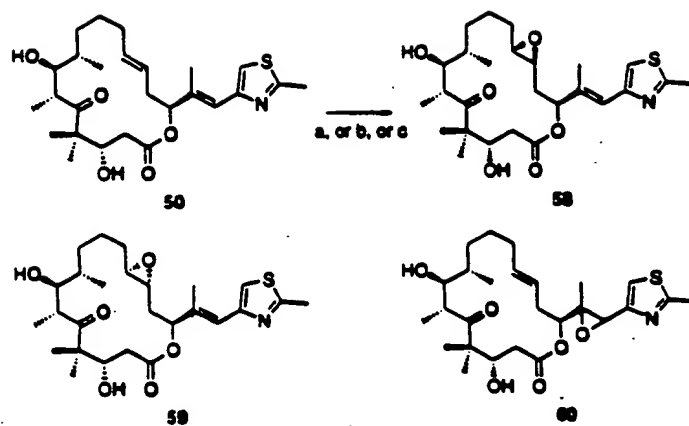
FIGURE 12

FIGURE 13

FIGURE 14

SBTO ⟶ —X   OTBS 82   ⟶ c
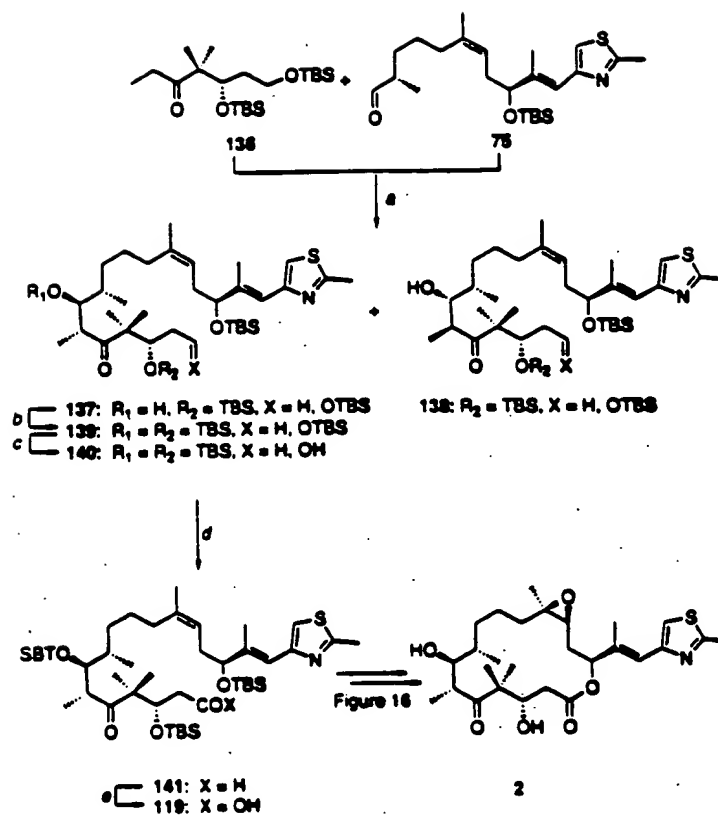
a ⊏ 99: X = OH
  ⊏ 113: X = I
b ⊏ 114: X = PPh₃ ⁺I⁻

101
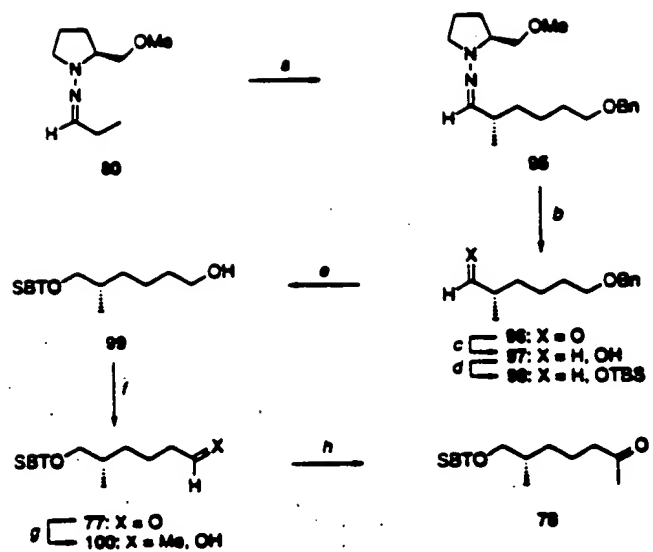
FIGURE 15

FIGURE 16

FIGURE 17

FIGURE 18

FIGURE 19
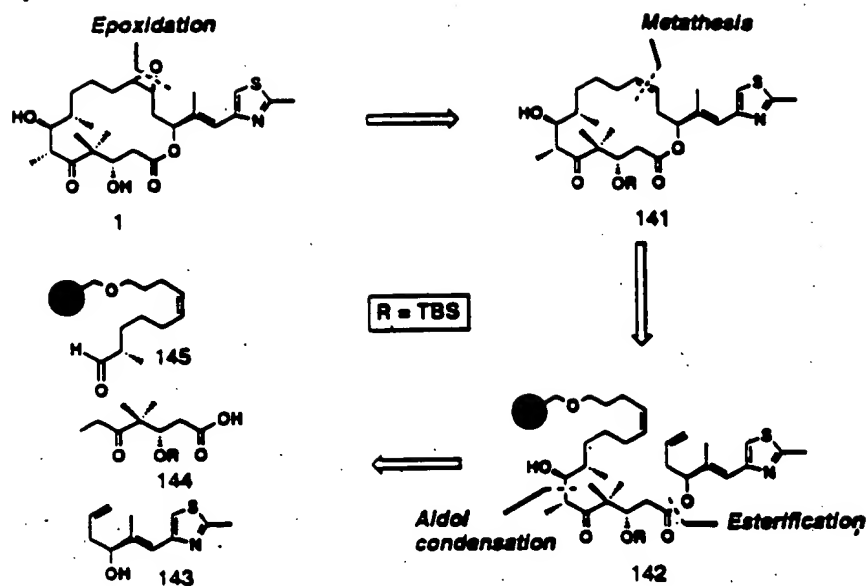
FIGURE 20
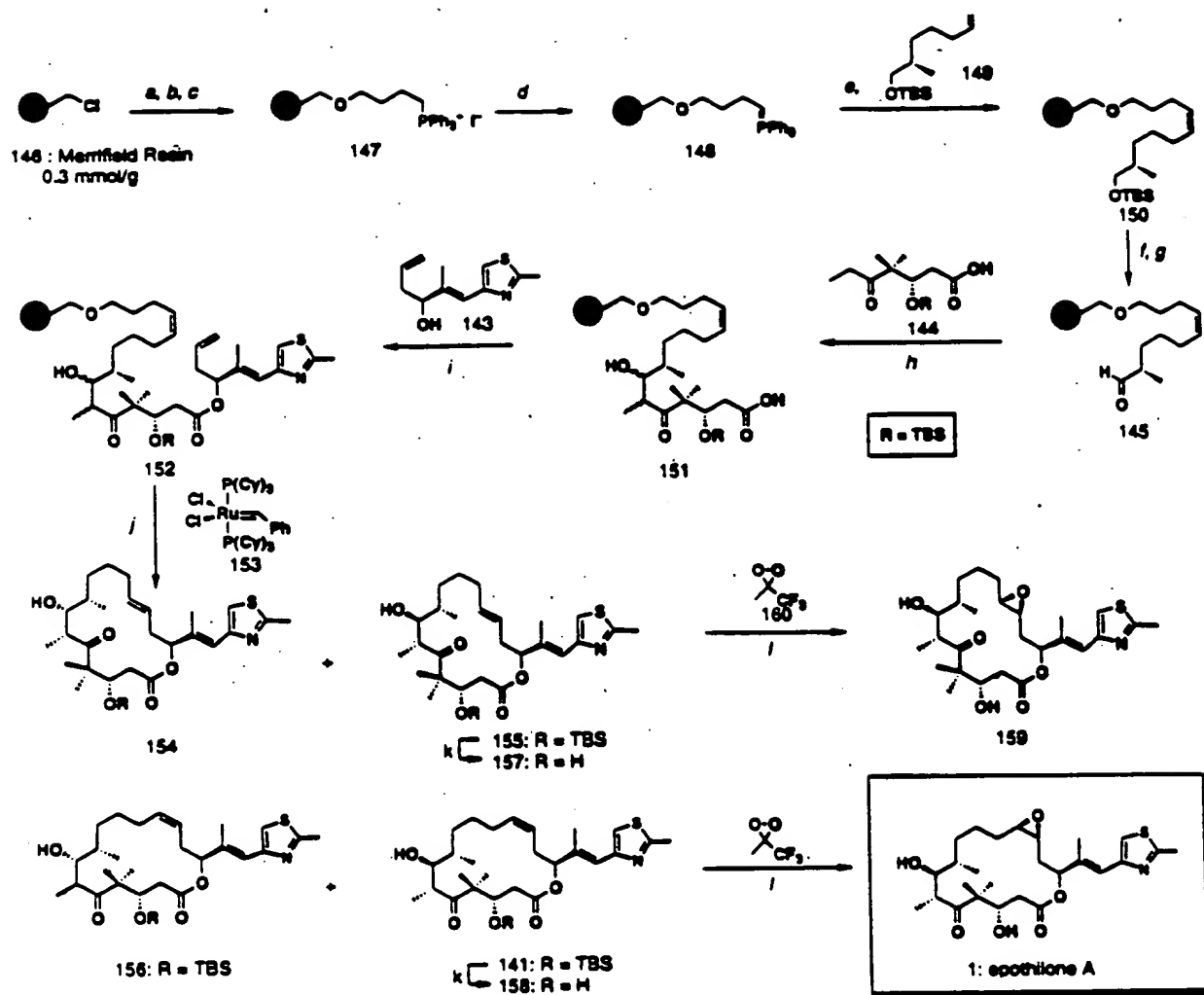
FIGURE 21
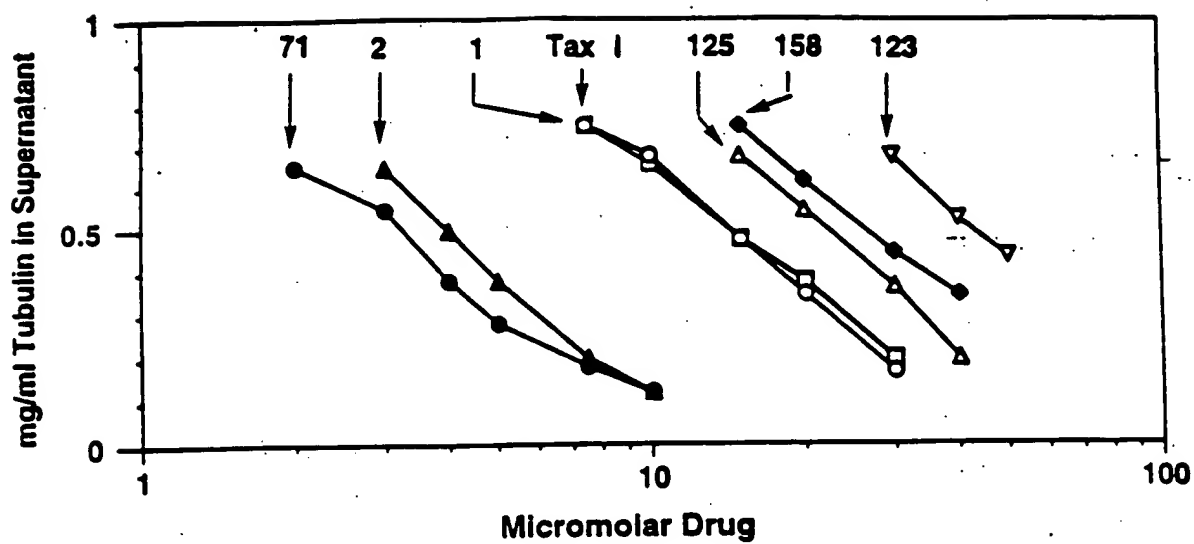
FIGURE 22

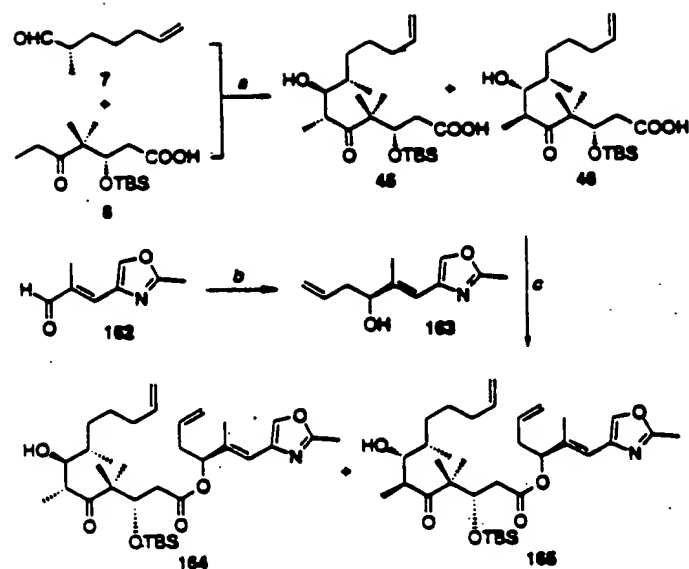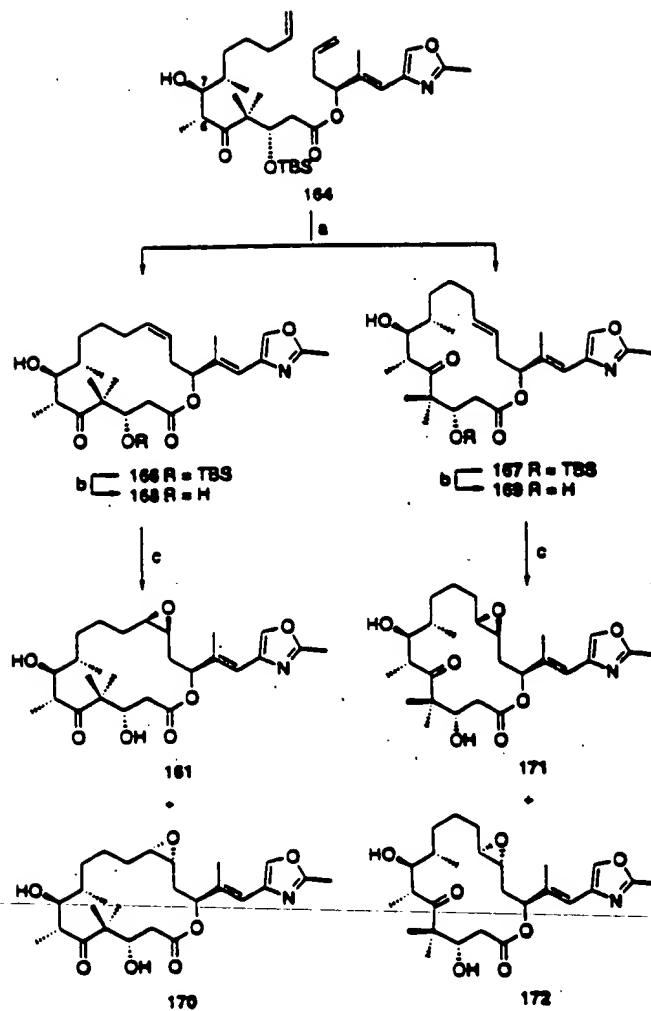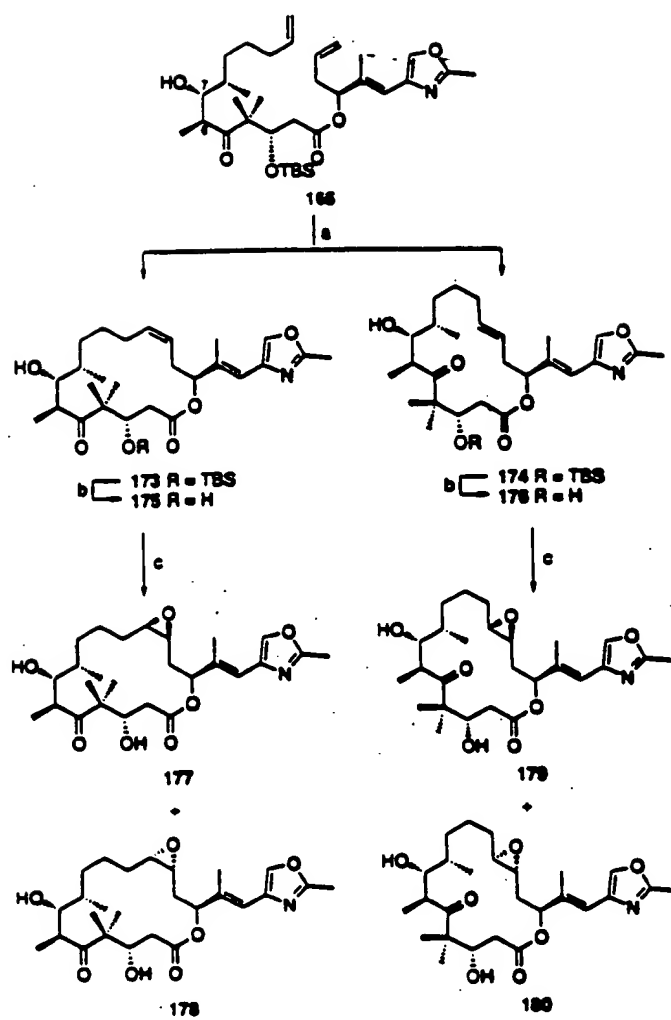| Compound	Induction of tubulin assembly[a]	Parental	Inhibition of human ovarian carcinoma cell growth[b]			
			Taxol-resistant			MDR-line
			β-tubulin mutants			
		1A9	1A9PTX10		1A9PTX22	A2780AD
	EC_{50} (mM) ± s.d.		IC_{50} nM (relative resistance)			
1	14 ±0.4	2.0	19 (9.5)		4.2 (2.1)	2.4 (1.2)
2	4.0 ±0.1	0.040	0.035 (0.88)		0.045 (1.1)	0.040 (1.0)
71	3.3 ±0.2	2.0	33 (17)		3.5 (1.8)	1.5 (0.80)
158	25 ±1	25	>100 (>4)		75 (3.0)	22 (0.88)
123	39 ±2	48	>100 (>2)		75 (1.6)	24 (0.50)
125	22 ±0.9	3.5	30 (8.6)		5.5 (1.6)	3.0 (0.86)
Taxol	15 ±2	2.0	50 (25)		43 (22)	>100 (>50)

FIGURE 23
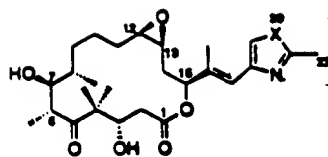
1: X = S: epothilone A
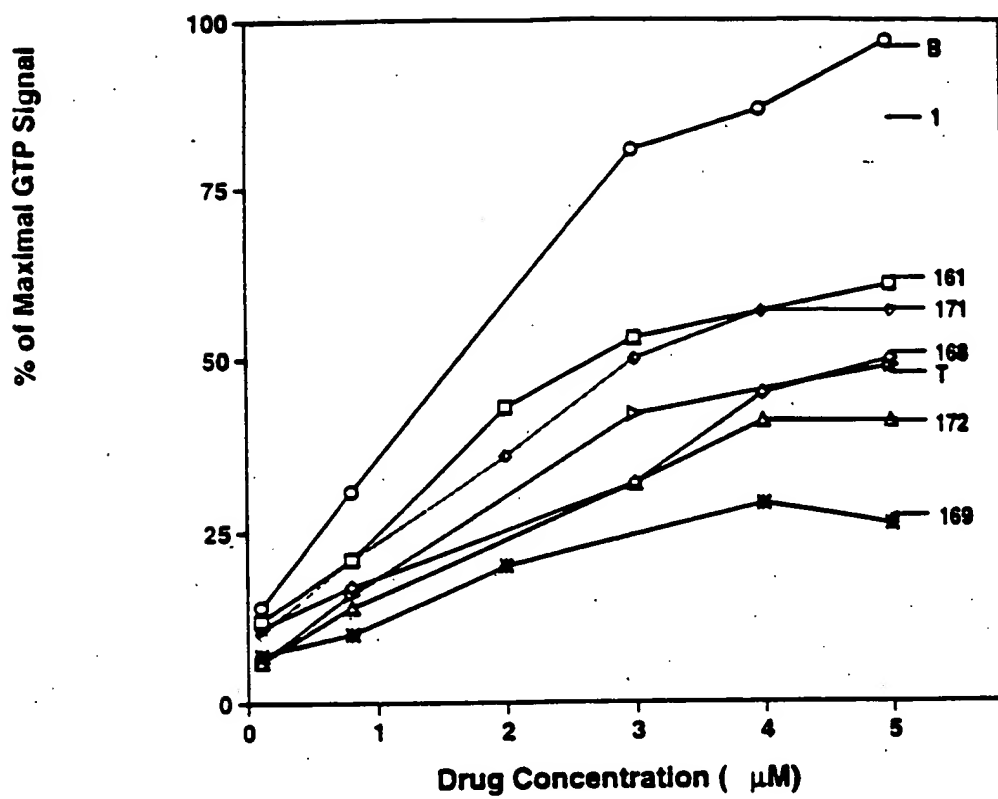161: X = O: epoxazone A

Figure 24

FIGURE 25

FIGURE 26

FIGURE 27

FIGURE 28

FIGURE 29

FIGURE 30

FIGURE 31

NaHMDS (1.5 eq.),
THF, 0 °C, 15 min.

−20 °C, 12 h, 73% (Z : E ca 1 : 1)

220

221

222

CSA (1.0 eq.),
CH₂Cl₂:MeOH (1 : 1),
0 °C, 1.5 h, 97%;

224

SO₃.pyr. (2.0 eq.), DMSO (10 eq.),
Et₃N (5.0 eq.),

CH₂Cl₂, 25 °C, 0.5 h, 95%.

223

LDA (3.0 eq.), THF, 0 °C, 15 min;
then 225 (1.2 eq.) in THF, −78 → −40 °C,
0.5 h; then 224 (1.0 eq.) in THF at −78 °C,
(ca 1 : 1 ratio); TBSOTf (3.0 eq.), 2,6-lutidine (3.0 eq.),
CH₂Cl₂, 0 °C, 2 h; K₂CO₃ (2.0 eq.), MeOH, 25 °C, 15 min,
31% of 226 and 30% of 6S,7R-diastereoisomer 227 from 224

225

226

TBAF (6.0 eq.)

THF, 25 °C, 8 h, 75%

228

227

2,4,6-trichlorobenzoylchloride
(1.3 eq.), Et₃N (2.2 eq.), THF,
0 °C, 1 h; 4-DMAP (10. eq.),
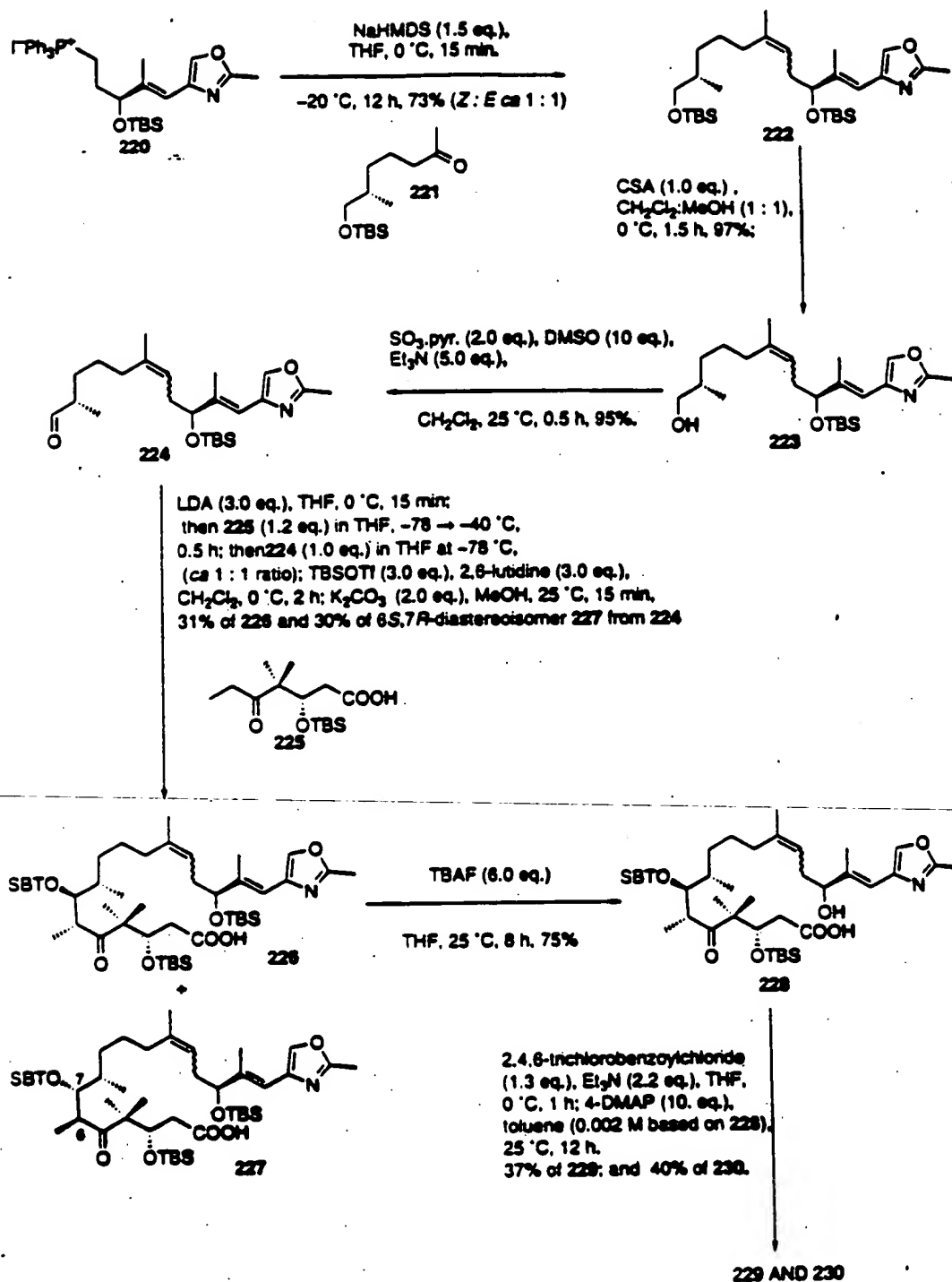toluene (0.002 M based on 228),
25 °C, 12 h.
37% of 229; and 40% of 230.

229 AND 230

FIG. 32

FIGURE 33

FIGURE 3A

FIGURE 35

250

229

FIGURE 36

FIGURE 37

TrtO

ethyl...OTBS / OTBS reagent

LDA (1.2 eq.), THF (x.x M),
0 °C, 15 min; 1 hr, xx%

257

HO

258

TBSOTf (1.2 eq.),
2,6-lutidine (2.0 eq.),
CH₂Cl₂ (0.1 M), 0 °C, 2 h, 96%

SBTO ... OTBS OH
260

CSA (1.0 eq.),
CH₂Cl₂:MeOH (1:1),
0 → 25 °C, 1.5 h, 85%;

SBTO ... OTBS OTBS
259

(COCl)₂ (2.0 eq.), DMSO (4.0 eq.),
Et₃N (4.0 eq.), CH₂Cl₂ (0.1 M),
−78 → 0 °C, 1.5 h, 95%;

SBTO ... CHO OTBS
261

NaClO₂ (3.0 eq.),
2-methyl-2-butene (3.0 eq.),
NaH₂PO₄ (3.0 eq.),
ᵗBuOH:H₂O (5:1), 25 °C, 2 h,
90%.

SBTO ... OTBS CO₂H
262

TBAF (6.0 eq.)
THF (0.1 M)
25 °C, 10 h
92 %

TrtO

SBTO ... OTBS O
264

2,4,6-trichlorobenzoylchloride
(1.3 eq.), Et₃N (2.2 eq.),
THF (0.07 M), 0 °C, 1 h;

then add to a solution of 4-DMAP
(10.0 eq.) in toluene (0.002 M), 25 °C,
6 h, x%

SBTO ... OH CO₂H
263

FIGURE 38

HF.Pyr (0.25%),

THF (0.05M)

methyl(trifluoromethyl)dioxirane,
MeCN, 0 °C,
85%

264

265

266

FIGURE 39